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IN THE CIRCUIT COURT OF THE  
11th JUDICIAL CIRCUIT, IN AND  
FOR DADE COUNTY, FLORIDA

1  
Jenny (as)  
Turbiner  
Carol-orig.  
1/12/98

CASE NO. 94-08273 CA (20)

HOWARD A. ENGLE, M.D., et al.,

Plaintiffs.

v.

R.J. REYNOLDS TOBACCO COMPANY,  
et al.,

Defendants.

1221 Brickell Avenue  
Miami, Florida  
December 11, 1997  
Thursday, 2:40 P.M.

DEPOSITION OF HUGH GILMORE, M.D.

Taken before Richard O. Applebaum,  
Shorthand Reporter, Notary Public for the State of  
Florida at Large, pursuant to Notice of Taking  
Deposition filed in the above cause.

KLEIN, BURY & ASSOCIATES, INC.

51960 3425

1 APPEARANCES:

2  
3 STANLEY ROSENBLATT, P A.  
4 By: JOHN HOAG, ESQUIRE  
on behalf of the Plaintiff.

5 SHOOK, HARDY & BACON  
6 By: DONALD KEMNA, ESQUIRE  
7 By: RICHARD MOLLISON, ESQUIRE  
8 By: NANCY JOHNSON  
on behalf of the Defendant/Lorillard.

9 CARLTON, FIELDS  
10 By: DOUGLAS CHUMBLEY, ESQUIRE  
11 on behalf of the Defendant/RJ Reynolds.

12 DECHERT, PRICE & RHOADS  
13 By: WILLIAM DODDS, ESQUIRE  
14 on behalf of the Defendant/Philip Morris.

15 in

HUMPHREY

16  
17  
18 I N D E X

19 WITNESS

DIRECT

CROSS

20 Hugh Gilmore, M.D.

3

--

1 Thereupon:

2 HUGH GILMORE, M.D.

3 was called as a witness on behalf the Defendant and,  
4 having been first duly sworn, was examined and  
5 testified as follows:

6 DIRECT EXAMINATION

7 Q. (By Mr. Hoag) State your name for the  
8 record, please.

9 A. Hugh Gilmore.

10 Q. First name is Hugh?

11 A. H-U-G-H.

12 Q. And have you ever been deposed before?

13 A. Yes, I have.

14 Q. How many times?

15 A. A lot. Over 30.

16 Q. Over 30?

17 A. Is it even more than over 30, like 40,  
18 50?

19 A. Probably, yes.

20 Q. You're talking about over a -- what  
21 period of time?

22 A. Twenty-five years.

23 Q. Is that since you've been a physician?

24 A. Since I've been in practice, in private  
25 practice.

1 Q. How many times have you been deposed in  
2 tobacco-related cases?

3 A. Never. This is the first time.

4 Q. The other cases that you were deposed in,  
5 what were they about?

6 A. They're almost all workmen's  
7 compensation.

8 I practice cardiology.

9 They usually are related to workmen's  
10 compensation.

11 Q. And specifically as it relates to  
12 cardiology and nothing else?

13 A. Yes.

14 Q. This would be related to individual  
15 claims that people would have?

16 A. Yes.

17 Q. Is this the first class action lawsuit  
18 you've ever testified in?

19 A. Yes.

20 Q. When I say class action, do you know what  
21 I mean?

22 A. Vaguely. It represents a lot of people,  
23 most of whom are not here. You pick a few people and  
24 say that they represent a class of people.

25 Q. Now, you've been listed as an expert

1 witness in the Engle case.

2 Do you know what the Engle case is about?

3 A. It's about somking-related diseases.

4 But I really know only the case of

5 Frosene Stevens.

6 Q. So you've looked at one medical file, and  
7 that's Frosene Stevens' medical file?

8 A. Yes.

9 Q. Have you looked at anything else to  
10 prepare yourself for this deposition today?

11 A. I have some reprints that were sent to me  
12 as part of the cases.

13 Q. Okay.

14 A. And there's a deposition of Frosene  
15 Stevens.

16 Q. What reprints were sent to you or  
17 provided to you?

18 A. I have them.

19 Q. Should I name them?

20 Q. Please.

21 A. Evaluating Coronary Heart Disease Risk by  
22 Hoeg, H-O-E-G; Inflammation, Aspirin, and the Risk of  
23 Cardiovascular Disease in Apparently Healthy Men, by  
24 Ridker, R-I-D-K-E-R; Changing Mortality from Coronary  
25 Heart Disease among Smokers and Nonsmokers over a

1 20-Year Interval, by Scheidt, S-C-H-E-I-D-T; Chronic  
2 Infections and Coronary Heart Disease, Is Three a  
3 Link? By Danesh, D-A-N-E-S-H; Commentary on Can We  
4 Treat Coronary Artery Disease with Antibiotics? It's  
5 an editorial. Inflammation, Atherosclerosis and  
6 Ischemic Events - Exploring the Hidden Side of the  
7 Moon, from the New England Journal, Maser, M-A-S-E-R.

8 Q. And who provided you with those?

9 A. Shook, Hardy and Bacon.

10 Q. The law firm?

11 A. Yes.

12 Q. Do you remember who it was from that law  
13 firm that provided you with those?

14 A. No.

15 Q. How long ago were you provided with  
16 those?

17 A. Less than three months. I would say two  
18 months.

19 Q. Did you specifically request those  
20 articles?

21 A. No.

22 Q. Do you know who selected those articles  
23 to provide to you?

24 A. No.

25 Q. Can I see those?

1 A. (Witness proffers.)

2 Q. All these articles appear to have been  
3 published in 1997; is that accurate?

4 A. I believe that's true.

5 Q. Do you have files with any other articles  
6 related to coronary heart disease?

7 A. No.

8 Q. So these articles that you've just named  
9 are the only articles you have in your files that are  
10 journal articles and/or letters concerning - letters  
11 and journal articles concerning heart disease; is that  
12 correct?

MR. CHUMBLEY: Object to the form.

13  
14 A. These are the only articles I have that  
15 were sent to me relative to this case.

16 I don't have any files of articles at  
17 all.

18 Q. Are you relying on these articles in any  
19 way for any portion of your expert testimony?

20 A. I read the articles. My opinions were  
21 formed before I read those. I read those to increase  
22 my fund of knowledge.

23 I don't believe these articles influenced  
24 my opinion.

25 Q. Did you bring anything else with you

1 today?

2 A. I have the deposition, the records of  
3 Frosene Stevens, and the amount of money I've been  
4 paid for reviewing these records.

5 Q. I'd like to see that.

6 A. (Witness proffers.)

7 Q. What I'm looking at now is, I guess, your  
8 billing record for review of medical records. It says  
9 six hours of medical records review.

10 Is this the extent of your billing to  
11 date to your client in this particular case, meaning  
12 the Engle case?

13 There's a conference that's not included.

14 It's the extent of the record review.

15 Q. So there's other billing --

16 A. There's another bill for a conference. I  
17 don't remember for how many hours, probably four hours  
18 of conference.

19 Q. Those articles that you've just named,  
20 I'd like to get them marked as an exhibit, composite  
21 Exhibit, Composite Exhibit One for purposes of this  
22 deposition.

23 Now, the billing record that you showed  
24 me, I'd like to get that marked, too, as Exhibit Two.

25

1 (Whereupon, the above referred to  
2 documents were marked as Plaintiff's Exhibits  
3 Nos. One and Two for Identification.)

4 Q. The first date on the medical record  
5 review is March 7, 1997.

6 Was that on or about the time you were  
7 first asked to review the medical records for Frosene  
8 Stevens?

9 A. Yes.

10 Q. Who asked you to do that?

11 A. Shook, Hardy and Bacon.

12 Q. Which is the law firm representing one or  
13 more of the tobacco companies; correct?

14 A. Yes.

15 Q. Do you know which tobacco companies they  
16 represent?

17 A. No, I don't.

18 Q. Do you know which attorney from Shook,  
19 Hardy and Bacon requested that you review Frosene  
20 Stevens medical records?

21 A. No, I don't.

22 Q. Do you know why you were asked to review  
23 her medical records?

24 A. To form an opinion regarding the  
25 relationship between tobacco smoke and heart disease.

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1 Q. Did you specifically request her medical  
2 records or did someone select those medical records to  
3 provide to you?

4 A. Somebody else selected them and provided  
5 them.

6 Q. Do you know how many depositions of class  
7 representatives have been taken so far in the Engle  
8 case?

9 A. No.

10 Q. Do you know how many medical records of  
11 different class representatives have been provided to  
12 defense counsel in the Engle case?

13 A. No.

14 Q. Do you know why the only medical records  
15 you were asked to look at was the medical records of  
16 Frosene Stevens?

17 A. No.

18 Q. Other than the deposition of Frosene  
19 Stevens, did you read any other depositions in any  
20 other case or in the Engle case to prepare yourself  
21 for this deposition today?

22 A. No.

23 Q. I think you answered it, but you have -  
24 you are not serving as an expert in any other  
25 tobacco-related case at this time; is that correct?

1 MR. KEMNA: Objection.

2 To the extent that your question may  
3 request information on matters that Dr. Gilmore  
4 is acting as a consultant but not a testifying  
5 expert or disclosed expert witness, I instruct  
6 him not to answer.

7 To the extent that he can recall any  
8 other matter where he has been formally  
9 disclosed as an expert, he may answer the  
10 question.

11 A. This is the only case that I'm listed as  
12 an expert.

13 I was listed as an expert on a case  
14 having to do with a Medicaid payments.

15 Q. When were you first contacted to be an  
16 expert or a consultant in any medical - in any  
17 tobacco-related case?

18 A. I believe January, '96.

19 Q. Who contacted you at that time?

20 A. Shook, Hardy and Bacon.

21 Q. Do you remember what attorney or  
22 attorneys contacted you?

23 A. No, I don't.

24 Q. Do you know how you came to be contacted?

25 A. No, I don't.

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1 Q. Do you know anyone --

2 Prior to the time that you were contacted  
3 by Shook, Hardy and Bacon, did you know anyone who  
4 worked at Shook, Hardy and Bacon?

5 A. No.

6 Q. Do you know anyone who works for any  
tobacco company?

8 A. No.

9 Q. By that I'm also including whether or not  
10 you know anyone who works for any law firm that  
11 represents a tobacco company?

12 A. No.

13 Q. Have you ever done any research --  
14 Withdraw that.

15 Have you ever published any research  
16 that's related in any way to tobacco and health?

17 A. No.

18 Q. Other than the research you've done since  
19 being contacted by Shook, Hardy and Bacon in 1996, had  
20 you done any literature review or research of any kind  
21 whether it was published or not that was related in  
22 any way to tobacco and health?

23 A. Never done any research.

24 If you mean have I ever reviewed papers  
25 or read papers, I read the standard cardiology medical

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1 journals, some of them dealing with tobacco and  
2 health.

3 Q. What medical journals do you read?

4 A. I read the cardiology journals, American  
5 Heart Journal, New England Journal.

6 Q. When you say that you read the cardiology  
7 journals, what journals are those?

8 A. The American College of Cardiology and  
9 Circulation, American Heart Association.

10 Q. You read those on a regular basis?

11 I would say fairly regularly. We get  
12 them in the library and I go to the library nearly  
13 every day and scan the journals.

14 Q. So are you saying to the extent that  
15 there were any articles in any of those journals  
16 related to tobacco and health, you would most likely  
17 have at least seen those prior to the time you were  
18 contacted by Shook, Hardy and Bacon?

19 A. Well, I won't say that I saw most of  
20 them. I've scanned the indexes and I read the  
21 articles that I think are pertinent to my practice.  
22 That would be true before they contacted me and since  
23 they've contacted me.

24 Q. Okay. You've been practicing cardiology  
25 for approximately 45 years?

1 A. It's not really 45. I finished medical  
2 school in '50 and I went into private practice in '69.  
3 I've been practicing privately since 1969. I worked  
4 full time at the medical school as a cardiologist from  
5 56 to '69. That's the University of Miami Medical  
6 School.

7 Q. What is your date of birth?

8 A. 1926, February 4th.

9 Q. Where is your private practice located?

10 A. I'm in the west building at Cedars  
Medical Center.

11 Q. Do you still do any teaching?

12 A. Yes.

13 Q. On a part-time basis?

14 A. It's volunteering.

15 Q. What's the nature of the teaching you do  
16 now?

17 A. I give a lecture to the students on risk  
18 factors in coronary heart disease. It's to the  
19 students who are electing to rotate through  
20 cardiology. It occurs about once a month, probably  
21 not that often, maybe once every five weeks.

22 Q. How long does that lecture last?

23 A. One hour.

24 Q. Do you use any materials?

1 A. No.

2 Q. Just kind of off the top of your head?

3 A. It's informal. I ask them, we go through  
4 it off the top of my head.

5 Q. What are the risks factors for coronary  
6 heart disease?

7 A. Are there?

8 Q. What are they?

9 They are things that have shown a  
10 statistical relationship to an increased incidence in  
11 heart disease.

12 Do you want me to name them?

13 Yes.

14 Age; gender; family history; smoking;  
15 hypertension; abnormal lipids; abnormal glucose  
16 tolerance; high uric acid. There are others, but  
17 those are the most widely recognized.

18 Homocysteine, I guess we should put down  
19 now. Homocysteine is another one.

20 Q. Is that all of the major ones that you're  
21 aware of?

22 A. Those are the big ones.

23 Q. When you say big ones, what do you mean?

24 A. That means that play - that they are  
25 either well studied or that they have a substantial or

1 significant statistical association.

2 Q. In family history, what do you  
3 specifically look for?

4 A. The presence of heart disease in a parent  
5 or sibling, but usually it's the parents.

6 Q. When you say usually it's the parents,  
7 what do you mean?

8 A. The siblings are usually disease free and  
9 the parents usually have the disease when the family  
10 history is positive. Sometimes the siblings are  
11 positive as well, but it's the parents that are the  
12 major risk factor.

13 Q. When you say the major risk factor, can  
14 you quantify that?

15 A. No.

16 Q. Let me clarify what I mean when I say  
17 quantify it. Two, three, ten, like for smoking under  
18 certain circumstances the risk factor might be as high  
19 as 20 or more; correct?

20 A. No. I don't know what you mean by 20 or  
21 more.

22 Q. For lung cancer?

23 A. I thought you meant heart disease.

24 Q. To explain what I mean I'm using that as  
25 an example.

1 A. I see.

2 I understand then.

3 I mean that the relative risk would be  
4 20 times more in smokers than in nonsmokers.

5 Q. Under certain circumstances, would you  
6 agree that that's true?

7 A. Yes.

8 Q. So as far as family history is concerned,  
9 one or more parents having a history of heart disease,  
10 can you quantify that in the same manner it can be  
11 quantified for a smoker and lung cancer?

12 MR. KEMNA: Objection to the form.

13 You really can't, because it depends on  
14 the age at which the parent developed the disease and  
15 it depends on whether it's a modifiable or a  
16 non-modifiable risk factor in the parents.

17 I don't know of any literature that  
18 documents the relative risk of having a parent with  
19 coronary heart disease.

20 Q. Unless you divide it down further by  
21 looking at the age, history, and whether they have a  
22 modified risk factor?

23 MR. KEMNA: Objection to the form.

24 Q. Is that right?

25 A. Yes.

1 If it were possible to do that.

2 I don't think it's possible to do that;  
3 that is, in most of the studies they say well, if the  
4 father had definite coronary heart disease or probable  
5 or he's still living after the age of 65, he probably  
6 didn't have it.

7 It's a guessing game. There are no  
8 reliable figures that I know of to give you a relative  
9 risk.

10 Q. Do they also look at - when you say  
11 modified or modifiable, do you mean, for example, if a  
12 family member had heart disease but was also a heavy  
13 smoker, if they didn't smoke it would have been  
14 modifiable is that what you mean?

15 A. Exactly.

16 Smoking is considered a modifiable risk  
17 factor.

18 Q. So smoking is considered a modifiable  
19 risk factor?

20 A. Yes.

21 Q. So when you look at family history, you  
22 would also - family history of heart disease or  
23 coronary heart disease, you'd want to look at whether  
24 or not the family member who had the heart disease was  
25 a smoker?

1 A. Right. Whether he was a smoker or not.

2 Q. Would there be anything else you'd want  
3 to look at?

4 A. Yes. All the risk factors I named.

5 You'd like to know whether he has high  
6 cholesterol, abnormal lipids, diabetes, overweight,  
7 sedentary activities, et cetera.

8 Q. Is there any particular sibling that  
9 makes it more likely - not sibling.

10 Is there any particular parent, father or  
11 mother, that makes it more likely that one will  
12 contract heart disease as a child?

13 MR. KEMNA: Objection to the form.

14 A. Not to my knowledge.

15 Q. I want to make sure that you understand -  
16 I think you did understand, but let me make sure.

17 By that I mean, if the person's mother  
18 was - had a history of heart disease, is it more  
19 likely that the child will have heart disease than if  
20 the person's father had heart disease?

21 MR. KEMNA: Objection to the form.

22 A. Again, I think I understand what you  
23 mean.

24 Comparing the two parents, not that the  
25 child has the heart disease but will develop heart

1 disease, again, my answer is, I don't believe there is  
2 any difference. I don't know of any studies that have  
3 shown that difference.

4 Q. Now, the second one you mentioned was  
5 smoking.

6 Can you quantify the risk factor for  
7 smoking and heart disease?

8 MR. KEMNA: Objection to form.

9 MR. CHUMBLEY: Join.

10 A. I can tell you the relative risk, which  
11 is generally, you compare smokers to nonsmokers and  
12 it's usually people who smoke a pack a day, and the  
13 relative risk ranges from 1.3 to 1.8 or 9.

14 Q. That would be for people who smoke one  
15 pack a day?

16 A. The studies generally would be, yes, one  
17 pack a day.

18 Q. And it depends on how many years they've  
19 smoked?

20 MR. KEMNA: Objection to the form.

21 A. It does depend on that, yes.

22 But I can't give you a time period that's  
23 critical.

24 Q. Why are you unable to do that?

25 A. I don't believe that the studies have

1       been able to show a cumulative effect.

2                       The risk factors for smoking are  
3       primarily in current smokers and it's less related to  
4       their past exposure to smoking.

5               Q.     I'm not totally sure what you just meant  
6       by what you said. Let me try to rephrase it and tell  
7       me if I'm understanding it.

8               A.     Sure.

9               Q.     If a person is a smoker right now, if  
10       they're smoking one pack a day right now, it's really  
11       not very significant whether they've smoked for 20  
12       straight years or ten straight years or five straight  
13       years, the significant factor is whether they're  
14       smoking right at the time they have or contract heart  
15       disease, is that what you said?

16              MR. KEMNA: Objection to the form.

17              A.     I'm saying that the most important factor  
18       - yes, I'm in general agreeing with that, that the  
19       risk of smoking is primarily related to the current  
20       smoking.

21                       Now, how did we arrive at the diagnosis  
22       of heart disease?

23                       One of the definitions of coronary artery  
24       disease is sudden death, people who drop dead suddenly  
25       are presumed to have coronary disease. They're

1 included in these studies in which you're saying they  
2 had coronary disease. So, in other words, it doesn't  
3 have to be chronic 20 years, it can be current.

4 Q. So you don't know of any increase in risk  
5 for a smoker who has smoked 30 years as opposed to a  
6 smoker who just started to smoke two days ago, as far  
7 as risk of contracting any form of heart disease?

8 MR. KEMNA: Objection.

9 Is that correct?

10 A. Well, - obviously there's no studies  
11 who have shown people who have smoked two days versus  
12 people who have smoked 20 years.

13 The general gist of your question is,  
14 does duration play a role in coronary artery disease  
15 risk?

16 I believe that it does play a role, but  
17 that role is modified by the current status. If he'd  
18 smoked for 20 years and then stops for a year, it  
19 changes the relative risk.

20 Q. And in what way does it change the  
21 relative risk if one stops for a year?

22 A. The relative risk goes down.

23 Q. By how much?

24 A. Well, it's thought that within two years  
25 the relative risk may be almost as much as if you

1 never smoked at all. So, in other words, over a  
2 period of two years most of the risk is probably gone.

3 Q. But if you don't ever really stop smoking  
4 for any reasonable length of time, then the duration  
5 of the smoking does increase the likelihood of heart  
6 disease; is that correct?

7 MR. KEMNA: Objection to form.

8 A. I believe that's true.

9 Q. How about the amount that you smoke; for  
10 example, you talked about one pack a day and what  
11 you've described or discussed as being the relative  
12 risk of between 1.3 to 1.8 to 1.9 for one pack a day.

13 Does it change if someone averages two  
14 packs of cigarettes per day?

15 MR. KEMNA: Objection to form.

16 A. I believe it changes, but I can't give  
17 you figures.

18 Q. Do you have any ballpark estimate of what  
19 the figures would be if one averages two packs of  
20 cigarettes per day?

21 A. No, I don't.

22 Q. How about three packs of cigarettes a  
23 day, is your answer the same?

24 A. The same.

25 Q. You know it's higher, but you don't know

1       how much higher; is that correct?

2                       MR. KEMNA:  Objection to the form.

3           A.     I don't know it.

4                       I believe that it's higher.

5           Q.     On what do you base that belief?

6           A.     Experience.  It seems to in me in my  
7 practice that patients who smoked more than a pack had  
8 a higher risk.

9                       What about hypertension?

10          A.     That's a risk factor.

11          Q.     And by hypertension, what do you mean?

12          A.     Elevated blood pressure.

13          Q.     Can cigarette smoking cause elevated  
14 blood pressure?

15          A.     I don't believe so, no.

16          Q.     Do you know if there's anything in  
17 cigarettes, nicotine or anything else, that causes  
18 elevated blood pressure?

19          A.     Well, nicotine temporarily in some people  
20 can increase blood pressure.

21          Q.     Okay.

22          A.     When I said temporarily, I mean while or  
23 for a short time after they smoke the cigarette.

24          Q.     If someone smokes cigarettes, chain  
25 smokes cigarettes throughout an entire day, do you

1 know whether or not that would elevate their blood  
2 pressure for the entire day?

3 A. First of all, it wouldn't occur in  
4 everybody.

5 In those people where this does occur,  
6 the more they smoke, the greater the exposure, and  
7 then they develop tolerance to the drug, nicotine, and  
8 they're less likely to have a chronically elevated  
9 blood pressure.

10 If you say a chain smoker smokes all day,  
11 I would say he probably doesn't have any change in  
12 blood pressure caused by the cigarette smoking or  
13 nicotine.

14 Q. Are you speculating or do you know that?

15 A. I think it's an individual thing.

16 I'm saying it's an educated estimate that  
17 most patients who chain smoke don't develop  
18 hypertension from chain smoking.

19 Q. Have you done - do you know if there's  
20 any research that verifies that?

21 A. No, I don't.

22 Q. So you're just guessing?

23 A. Yes.

24 Q. And can you quantify how hypertension  
25 increases in your opinion the risk for heart disease?

1 A. The relative risk again?

2 Q. Yes.

3 A. It's about the same. It's under two.

4 It's under two. It's a little bit more than cigarette  
5 smoking. Again, it depends on the duration and the  
6 elevation of the blood pressure.

7 Q. When you say two, what level of  
8 hypertension does that risk factor of approximate-  
9 two coincide with?

10 MR. KEMNA: Objection, form.

11 A. Greater than 150 and greater than 90,  
12 moderate hypertension.

13 Q. That's moderate.

14 What is higher?

15 I don't know how you rate it.

16 What do you call higher than moderate?

17 MR. KEMNA: Objection to the form.

18 A. It depends on age and somewhat on gender.

19 Usually over 170 would be more than  
20 moderate and for diastolic over 110.

21 Q. Does that increase the risk ratio or risk  
22 factor to more than two?

23 A. Yes, but I couldn't give you the figure.

24 Q. Again, all these questions I'm asking you  
25 are related to heart disease and no other diseases;

1 correct?

2 A. That's correct.

3 Coronary heart disease, really.

4 Q. So you think it's a factor higher than  
5 two, but you're not sure what it is?

6 A. I said it's around two.

7 Q. It still stays at around two?

8 A. H-huh.

9 Q. So that the elevated - once it gets to be  
10 a moderate level of hypertension, the risk doesn't  
11 change, as far as you know, if the hypertension level  
12 or the blood pressure level increases to above  
13 moderate is that correct?

14 A. No. It does increase, but I don't know  
15 the figure. I'll going to say around two is the  
16 figure that I know for across the board hypertension.

17 Q. Okay.

18 A. I don't know of any studies or figures  
19 documenting that the greater the blood pressure, the  
20 higher the risk.

21 Q. Abnormal lipids, what does that mean?

22 A. High cholesterol.

23 It counts a lot of different lipids. HDL  
24 and LDL, but we're just going to say abnormal lipids.

25 Q. Does it matter whether it's LDL or HDL?

1 A. HDL are thought to be protective and LDL  
2 is thought to be harmful, and total cholesterol is  
3 thought to be harmful. And there are other lipids  
4 that we don't generally measure that are thought to be  
5 harmful or beneficial.

6 Q. Is there anything in cigarette smoke that  
7 effects the cholesterol level in one direction or  
8 another?

9 A. No.

10 Q. What would be an abnormal lipid level?

11 A. If the cholesterol is over 200.

12 Q. The total?

13 A. Uh-huh.

14 Q. For the LDL, over 160.

15 Q. Okay.

16 A. And for the HDL, if it's under 30.

17 Q. If the HDL is significant higher than 30,  
18 that's a good thing?

19 A. Yes.

20 Q. A good thing meaning though it's  
21 abnormal, it actually decreases the risk for heart  
22 disease; is that correct?

23 MR. KEMNA: Objection to the form.

24 A. It decreases the risk.

25 Q. Even though it's abnormal for the HDL?

1           A.     When I say over 30 is normal, 65 to 70 is  
2     generally considered up to normal. That's still  
3     normal. Above that is within the upper five percent  
4     and, therefore, just by logically we think of the lower  
5     five percent and the upper five percent as abnormal.  
6     It doesn't mean necessarily bad.

7                     The answer to that question is, if it's  
8     over 65 or 70 it's probably abnormal, but because it's  
9     not average it's probably beneficial and not harmful.

10                    And how does the not beneficial abnormal  
11     lipid count fall out as far as the risk factor is  
12     concerned for heart disease?

13                   MR. KEMNA: Objection to the form.

14                   A.     The risk ratio has generally been said to  
15     be about two, also.

16                    There's now a lot of publicity and  
17     evidence saying that for every one percent change in  
18     the lipid, you get a two percent change in the risk of  
19     heart disease. So that if you lower the serum  
20     cholesterol by one percent, presumably you reduce the  
21     risk by two percent.

22                   Q.     To just put it in other terms, tell me if  
23     this is right, if you have a total count - for the  
24     lipids, if you have a total count of 150, that - would  
25     that then decrease your risk by 25 percent?

1 MR. KEMNA: Objection to the form.

2 A. I can't say that that's the way it's been  
3 done.

4 What you're saying makes sense based on  
5 what I said.

6 The way they're deriving this evidence is  
7 by saying if you lower the serum cholesterol from 300  
8 by 10 percent, which would be 30, that you would  
9 reduce the chance of getting a heart attack by 20  
10 percent.

11 The abnormal glucose tolerance --

12 A. That's diabetes.

13 So people that are diabetic are at  
14 increased risk for heart disease?

15 A. That's right.

16 If they have a family history of  
17 diabetes, they're at increased risk of heart disease.

18 Q. When you say family history, does that  
19 include siblings or are you just including mother and  
20 father?

21 A. It would be anybody, but mother and  
22 father would be the most important.

23 Q. When you say anybody, it would be  
24 grandparents --

25 A. Grandparent or sibling.

1 Q. Would it go any further than that?

2 A. Well, further than that it's so hard to  
3 document.

4 It would probably be important because it  
5 often skips generations. The grandparents are very  
6 important, but the great grandparents might not be so  
7 important.

8 Q. How much does that increase the risk  
9 factor?

10 A. I can't give you a figure. I don't know.

11 Q. Has that been published anywhere?

12 A. There are a lot of studies showing an  
13 increased risk. I don't remember any percentage  
14 statement relative risk.

15 Q. Do any of these - back up. I'm going to  
16 back up.

17 A. You've heard the concept of synergism?

18 A. Yes.

19 Q. What's your definition of synergistic?

20 A. That the sum of the parts is greater than  
21 just adding them together.

22 Q. For example, do you know whether people  
23 exposed to asbestos and people who are cigarette  
24 smokers are at greater risk for lung cancer than  
25 people who merely smoke cigarettes?

1 MR. KEMNA: Objection.

2 A. I'm not an expert on that.

3 I believe that to be true.

4 Q. That would be an example of synergistic  
5 effect; correct?

6 A. Well, in my mind synergism would mean  
7 that the incidence of people who smoke and have  
8 exposure to asbestos is greater than the incidence in  
9 those exposed only to asbestos plus those who are only  
10 exposed to cigarette smoke.

11 In other words, if the risk in asbestos  
12 exposure is five percent and smoking is five percent,  
13 and people who are exposed to asbestos and smoking  
14 it's not 10 percent, but it's 15 percent, that's  
15 synergism.

16 Q. Or it might be even higher than that?

17 A. It might be even higher than 15, but  
18 would be greater than ten.

19 Q. Do any of these risk factors that you've  
20 named for heart disease have a synergistic effect with  
21 one another?

22 A. It's thought that they do.

23 Q. All of them or just some of them?

24 MR. KEMNA: Objection.

25 A. I don't know.

1 Q. When you say it's thought that they do,  
2 what do you base that on?

3 A. Well, there are studies that show that if  
4 you have two risk factors it's greater than having the  
5 addition of the two individuals ones only.

6 There's a clustering of risk factors, so  
7 that people who have one risk factor often tend to  
8 have other risk factors, so it's hard for me to say  
9 that that's just synergism or whether if you added the  
10 two together. I don't know the answer.

11 Okay.

12 But there is a clustering.

13 Whether it's synergistic or not, I  
14 couldn't justify.

15 Q. You don't know - whatever the numbers may  
16 be, you don't know what they are?

17 A. That's correct.

18 Q. And whether it's all of these factors  
19 together or just some of them that are synergistic,  
20 you don't know that either; correct?

21 MR. KEMNA: Objection.

22 A. Right.

23 Q. You said that's correct, that you don't  
24 know; correct?

25 A. I do not know.

1 Q. I'm not sure I'm pronouncing this one  
2 right; high uric acid?

3 A. I just mean elevated uric acid.

4 I don't know the relative risk nor can I  
5 tell you the level at which it becomes a risk.

6 Q. Well, what is uric acid?

7 A. It's a product of protein metabolism. It  
8 probably represents an abnormality in protein  
9 metabolism. Uric acid probably represents an abnormal  
10 protein metabolism.

11 Q. If you know, what percentage of the  
12 general population suffers from high uric acid?

13 A. I don't know, but it's small.

14 Q. When you say small --

15 A. The common disease associated with high  
16 uric acid is gout.

17 It's simply a statistical correlation  
18 that people who have an elevated uric acid have a  
19 higher rate of coronary disease.

20 And no efforts have been made by medicine  
21 to screen people for high uric acid and give them a  
22 medicine to lower it as a preventative measure.

23 There's no evidence that reducing the  
24 uric acid lowers that risk factor.

25 Q. When you say that the percentage of

1 people with high uric acid is small, less than five  
2 percent?

3 A. Probably.

4 Q. Do you know whether it's less than one  
5 percent?

6 A. I think it might be one percent or two  
7 percent. That would be a guess.

8 Q. So for those perhaps one or two percent  
9 of the people in the general population with high uric  
10 acid, those people have a higher risk of heart disease  
11 than others, but you're not sure what that higher risk  
12 is, how much it is?

13 I don't know what it is, no.

14 Homocysteine, what is that?

15 A. It's another product of protein  
16 metabolism.

17 Q. And when you said homocysteine, is it  
18 high or low?

19 A. It's high.

20 The correlation between homocysteine  
21 levels and coronary artery disease is similar to the  
22 cholesterol story. If you're one standard deviation  
23 elevated with homocysteine, you have about the same  
24 risk of one standard deviation of serum cholesterol.  
25 The mechanism is not known, and I don't know the

1 frequency in the population.

2 Q. You don't know what percent of the  
3 population suffers from high homocysteine?

4 MR. KEMNA: Objection.

5 A. That's right.

6 Q. Do you know whether it's a small number  
7 or not?

8 A. I don't know the number. Nobody knows,  
9 to my knowledge, the number.

10 It's higher than uric acid and probably  
11 lower than cholesterol.

12 Q. How does one go about measuring the  
13 homocysteine level?

14 A. The laboratory can do a blood test. It's  
15 a new -- I won't say discovery because it's been there  
16 for years, but it's only this year becoming popular.  
17 The laboratory test is expensive and I don't think  
18 it's very reliable yet.

19 Q. So even if the test was done it wouldn't  
20 necessarily be accurate?

21 MR. KEMNA: Objection.

22 A. I'd be afraid to depend on just a single  
23 test. I'd rather repeat it and see.

24 Q. Did you have any even rough estimate of  
25 the percentage of the population that would have high

1 homocysteine, like is it five percent or less?

2 MR. KEMNA: Objection.

3 A. I think it might be five percent or more.

4 In other words, I don't know. People studying it have  
5 said this may be as big a risk factor as cholesterol.

6 Q. So it's a new area, as far as you know;  
7 correct?

8 A. Yes.

9 Q. You're not really familiar with the  
10 research, is that correct?

MR. KEMNA: Objection.

12 A. I read the current research.

13 The research is just taking off now, it's  
14 just beginning.

15 Q. Now, since we've been talking, are there  
16 any other additional risk factors --

17 A. I think I had put down gender and age,  
18 but they're not modifiable.

19 Q. You did?

20 A. I did put down sedentary activity.

21 Q. Lack of exercise?

22 A. Lack of exercise.

23 Q. Okay.

24 A. And I should mention obesity, although it  
25 may not be the obesity that's the risk, but it

1 identifies people who are at risk.

2 Q. When you say it may not be the obesity  
3 that's the risk, what do you mean?

4 A. Well, if you correct for their levels of  
5 lipids and if you correct for their inactivity and if  
6 you correct for their high blood pressure, it doesn't  
7 leave very many people who are purely obese to study.

8 Obesity as itself is a risk factor. It's  
9 associated with so many other risk factors, it's hard  
10 to pinpoint if it is due to obesity.

11 Q. Are you saying you don't know whether  
12 it's an independent risk factor, obesity?

13 MR. KEMNA: Objection.

14 I'm saying it is an independent risk  
15 factor, but it's probably not a very important one, if  
16 you correct all the other ones.

17 Q. If you correct all the other ones, what  
18 would be the risk ratio for obesity?

19 A. I don't know.

20 Q. And does it matter what the level of  
21 obesity is?

22 A. Yes.

23 Q. In what way does it matter?

24 A. The more obesity, the higher the risk.

25 Q. So if you're only ten pounds overweight,

1 the risk is going to still be there, but it's going to  
2 be small; is that what you're saying?

3 A. Exactly.

4 Q. Is it a linear progression?

5 MR. KEMNA: Objection.

6 Q. Twenty pounds overweight it's a little  
7 higher than ten, 30 is a little higher than 20, and on  
8 and on?

9 MR. KEMNA: Objection.

10 A. I don't think it's linear.

11 It does go up as you say. It's usually  
12 measured -- they usually describe it in figures called  
13 ponderal index, which is a figure derived from height  
14 and weight.

15 Based on that, it's probably steeper than  
16 linear; that is, a little bit of overweight just gives  
17 you a little bit of risk whereas when you begin to get  
18 big overweight, the risk probably goes up a little  
19 faster.

20 Q. What would be your definition quantifying  
21 it as big overweight?

22 MR. KEMNA: Objection.

23 A. 30 percent above ideal.

24 Q. So when you get to 30 percent or more  
25 above your ideal weight, your risk factor goes up -

1 it's a higher amount of increase?

2 MR. KEMNA: Objection.

3 A. I think so. I think so. It may still be  
4 more or less linear.

5 30 percent over ideal is obese enough to  
6 be a risk factor.

7 Q. Do you know how much of a risk factor it  
8 is?

9 Well, it increases as you get heavier,  
10 but I can't tell you how much.

11 Q. You couldn't really put a number on it?

12 I can't put a relative risk factor.

13 What about age?

14 It's a risk factor. I can't give you the  
15 relative risk. It increases with age; that is, an  
16 increase in age is an increased risk.

17 Q. And that's true for all forms of heart  
18 disease?

19 A. No.

20 Coronary disease, atherosclerotic heart  
21 disease.

22 Q. So the younger that you get - contract  
23 heart disease, the less likely it becomes that that  
24 particular risk factor was implicated; is that  
25 correct?

1 MR. KEMNA: Objection.

2 A. I don't believe so.

3 If you get heart disease at a young age,  
4 I think that that age was the risk. When he was  
5 younger, he didn't have the heart disease.

6 In other words, if you get a heart attack  
7 at the age of 25, I think the age of 25 was a risk  
8 factor. If you live to be 30, it would be a greater  
9 risk factor. It starts with birth.

10 Q. I'm just kind of thinking out loud to  
11 myself and I'll ask you, too, by that definition of  
12 age being a risk factor, then age would be a risk  
13 factor for everything always?

14 MR. KEMNA: Objection.

15 A. It would be a risk factor for coronary  
16 disease.

17 Q. What would then not be a risk factor for  
18 the definition that you've just given?

19 A. I don't think we're understanding each  
20 other.

21 I'm saying that no matter what age you  
22 get a heart attack due to coronary artery disease,  
23 that was a chronic progressive disease that took time  
24 to develop. Whatever time that is was a risk factor.  
25 The older you are, the greater the risk.

1 I don't mean that people who are 25 years  
2 of age have a high risk of getting heart disease.

3 Q. I guess what I'm asking is, do you mean  
4 that a person who does get - does have a heart attack  
5 or contracts heart disease of any kind at the age of  
6 25, that in your opinion their age was a reason as -  
7 was one of the causes of their heart disease?

8 MR. KEMNA: Objection to the form.

9 A. I'm not saying cause.

10 I'm saying it's riskier the older you  
11 are. If you got it at 25, it's clear that his risk at  
12 24 was less because he didn't have it then.

13 Q. Gender, how does gender fit into the  
14 picture?

15 A. Males have more heart attacks and  
16 coronary artery disease than females.

17 Q. Is that an independent risk factor being  
18 male, even taking into account all the other risk  
19 factors?

20 A. Yes.

21 Q. And what is the ratio?

22 A. I've never seen it published. I don't  
23 know what the risk is. It changes with age. Once a  
24 woman reaches menopause, that risk ratio returns  
25 towards one-to-one. In other words, after the age of

1 45 or 50, the danger of being a male compared to being  
2 a female becomes less and less and the risk ratio gets  
3 closer to one.

4 Q. Now, if more people who smoke are male,  
5 could that have anything to do with the fact that  
6 males are more likely to contract heart disease than  
7 females?

8 A. I don't think it does.

9 Q. What do you base that on?

10 A. The gender is an independent risk factor.  
11 Men and women who don't smoke when impaired, there's  
12 still the difference that men have more heart attacks  
13 than women.

14 Q. Are there any particular studies you're  
15 relying on to reach the conclusion you've just  
16 provided regarding risk factors for heart disease?

17 A. No particular study.

18 Q. Now, in your private practice, are you  
19 exclusively seeing patients who suffer from heart  
20 disease?

21 A. Not exclusively, but the bulk of my  
22 practice is patients with heart disease.

23 Q. When you say the bulk of your practice,  
24 what do you mean?

25 A. Over 80 percent, probably.

1 Q. Are they referred to you by other  
2 physicians?

3 A. Some of them. Some by other patients,  
4 some come in independently.

5 Q. Has that pretty much always been the  
6 percentage of your patients that suffer from heart  
7 disease, about 80 percent?

8 A. Yes

9 Q. And the other 20 percent, what are their  
10 problems?

11 A. Diabetes, arthritis, respiratory  
12 infections

13 Q. Do you ever treat anyone with lung  
14 cancer?

15 A. No.

16 Q. What percentage of your patients with  
17 heart disease were - smoked cigarettes on a regular  
18 basis at some time in their life?

19 MR. KEMNA: Objection to the form.

20 A. I don't know the percent. There are a  
21 lot of patients who smoked for a year or two. I would  
22 say that probably over 50 percent had smoked at some  
23 time in their life.

24 Q. And what percentage of your patients, and  
25 we may need to break this down by different, I don't

1 know, decades or years, it may have changed over time,  
2 but now as we speak, what percentage of the patients  
3 you see with heart disease are smokers at the time you  
4 first see them?

5 A. Again, I don't know, it's a guess, but  
6 I'll say probably 40 percent or 50 percent.

7 Q. And has that percentage changed over  
8 time; for example, ten years ago was it any more or  
9 less?

10 A. I think ten years ago it was more.

11 Q. What makes you believe that?

12 A. I think that they tell me; that is, my  
13 history from the patient is that more often people  
14 either ~~smoke~~ smoked or they have quit smoking by the  
15 time they come to see me. Of the patients who are my  
16 patients already, some of them have stopped, so the  
17 number of patients smoking is less.

18 Q. Okay.

19 A. And I think that reflects the general  
20 population, which shows a decrease in smoking of the  
21 general population.

22 Q. Do you know what the percentage for the  
23 general population is now of people who smoke?

24 A. No.

25 Q. Of those estimated 40 or 50 percent of

1 the people who come to you with heart disease who  
2 still are smokers at the time, do you give them any  
3 advice regarding their smoking?

4 A. Yes.

5 Q. What advice do you give them?

6 A. I tell them to stop smoking.

7 Q. And why do you give them that advice?

8 A. Because I want them to reduce their  
9 risks. I want them to be in the good risk group.

10 Q. What percentage of those people who are  
11 smokers at the time they first come to see you take  
12 your advice and stop smoking?

13 A. I think maybe 50 percent stop.

14 By the end of a year, I would guess at  
15 least half of those are back to smoking. At the end  
16 of a year maybe I have 25 percent of my patients who  
17 were advised to stop smoking have stopped.

18 Q. From your personal experience, do the  
19 people who come to you with heart disease who actually  
20 do stop smoking on the average live longer than those  
21 who continue to smoke?

22 MR. KEMNA: Objection.

23 A. I can't tell. I don't have that data.

24 Q. The 50 percent of the people who you  
25 advice to quit smoking who just don't do it, don't -

1 50 percent of them don't even make an attempt to quit  
2 smoking; is that correct, approximately?

3 A. Well, they may attempt it, but they don't  
4 ever stop.

5 Q. Totally?

6 A. Totally.

7 Q. Okay. Do they explain why they don't  
8 stop totally?

9 Some of them say they want to smoke.  
10 When told that they should stop, no, I smoked before,  
11 I like it. I'm going to keep smoking. Some of them  
12 try and say I felt stress or - so I started smoking  
13 and now I'm smoking.

14 Q. When you advise them to quit smoking, do  
15 you explain why to the patient?

16 A. I tell them that I'd like them to be in  
17 the good risk group, that is, to have a lower chance  
18 of getting progression of their disease or death.

19 Q. So if a patient says immediately at that  
20 point I like smoking, I just like to do it, do you say  
21 anything to them?

22 A. I say I can help you to stop smoking, I'd  
23 like to refer you to a clinic that will help you to  
24 stop smoking. And at the end of the discussion - on  
25 each visit I renew my offer to have them stop smoking.

1 There are some who won't.

2 Q. Now, do any of them say - even when you  
3 say like I can refer you to a place that will help you  
4 stop smoking, do any of them say I like it too much,  
5 no, I can't, do any of them say that?

6 MR. KEMNA: Objection.

7 A. Yes.

8 Q. And do you say anything else when they  
9 say that?

10 No.

11 Q. You just kind of figure they're going to  
12 do what they're going to do?

13 A. I say, can I dissuade you from smoking?

14 They say no, I'm going to keep smoking.

15 I say okay, next visit we'll talk about  
16 it again.

17 Q. And do you bring it up again?

18 A. I say, if you want to stop smoking, do  
19 you need help?

20 I don't tell them this every visit, I'm  
21 sure.

22 Every visit I say, are you smoking or not  
23 smoking? If they say they're smoking, I admonish them  
24 and offer them. If they say they have stopped  
25 smoking, I congratulate them and offer them support.

1 Q. And --

2 A. But in the patients who have told me I  
3 want to keep smoking, don't bother me every visit, I  
4 don't bother them every visit.

5 Q. Have you ever said something to the  
6 effect to any patient look, if you don't stop smoking,  
7 you are more likely to die of a heart attack?

8 A. I think that's what I'm saying. Your  
9 risk of dying of a heart attack or having progress in  
10 your disease is higher if you continue to smoke.

11 Q. Is it more likely than not that smoking  
12 cigarettes results in the premature death of at least  
13 some people?

14 MR. KEMNA: Objection.

15 A. No, I don't know that.

16 Q. Does cigarette smoking cause any disease?

17 A. I don't think that it's proven to cause  
18 heart disease.

19 Any disease, I couldn't answer.

20 Q. Let me - does cigarette smoking cause  
21 lung cancer?

22 A. That I don't.

23 Q. Does anything cause heart disease, as far  
24 as you know?

25 A. I don't know the cause, no.

1 Q. So you know something or some things  
2 cause heart disease, but you don't know what those  
3 things are?

4 MR. KEMNA: Objection.

5 Q. Is that correct?

6 A. I'd have to say that's a possibility.

7 But I don't know that a thing or some  
8 things are the cause.

9 When you say things, it includes so many  
10 options that I think what you say is certainly  
11 possible.

12 When you refer people to - people who say :  
13 I don't want to quit or I can't quit, when you refer  
14 them to places to help them, what are you referring  
15 them to?

16 A. Many of the hospitals in town have or  
17 there are private places that have a course to  
18 encourage and help people stop smoking.

19 Q. What is the nature of the course?

20 A. They point out to the people the high  
21 risk of continuing to smoke, the cost, financial, the  
22 harmful effects of smoking.

23 Q. Now, for heart patients would the  
24 nicotine patch be contraindicated?

25 A. No.

1 Q. It would be okay for them to use that --

2 A. Some of them get a reaction to it.

3 In general, patients who are stable can  
4 use the nicotine patch, yes.

5 Q. Do any of your patients use the nicotine  
6 patch?

7 A. Yes.

8 Q. Do you refer - have you ever had occasion  
9 to prescribe the nicotine patch for any of your  
10 patients?

11 A. Yes.

12 Q. How frequently do you prescribe it?

13 A. It's a small percent. I would say  
14 probably less than five percent.

15 Q. And why was it that small a percent, less  
16 than five percent?

17 I'm asking that because what you've  
18 described sounds like there's somewhere between 25 to  
19 50 percent of your smoking patients who have some  
20 trouble stopping, quitting smoking; is that correct?

21 MR. KEMNA: Objection.

22 MR. CHUMBLEY: Object to the form.

23 A. Yes.

24 Q. But yet you only prescribe or have  
25 prescribed the nicotine patch for about five percent

1 of those.

2 Why only five percent?

3 A. I offer it to patients. When patients  
4 want help, I offer them the patch. But they have the  
5 alternative of using gum or now there's an alternative  
6 of using a pill. The pill does not have nicotine.

7 I would say in the last six months I'm  
8 much more likely to use the pill Zyban than to use the  
9 nicotine patch.

10 Q. In the last few months?

11 A. Yes.

12 Q. Zyban's only been available for  
13 prescription for smokers under the name Zyban for  
14 about that long, right, for a few months?

15 A. Yes.

16 Q. And the patch, that doesn't require a  
17 prescription any more; correct?

18 A. I think you're right. I had forgotten,  
19 but I think you're right.

20 Q. And the - did the gum require a  
21 prescription?

22 A. It did, but I don't know if it does now.

23 Q. Your estimate is somewhere around five  
24 percent of those people who are having trouble  
25 quitting smoking who are your patients you prescribe

1 the nicotine patch.

2 What percentage would you prescribe or  
3 recommend nicotine gum?

4 MR. CHUMBLEY: Object to the form.

5 MR. KEMNA: Objection to the form.

6 A. Less than the patch, so one or two  
7 percent.

8 Q. And do you know whether or not it was  
9 effective in helping people to quit smoking?

10 MR. KEMNA: Objection.

11 I don't think that either the gum or the  
12 patch has been very effective; in other words, I think  
13 probably less than 50 percent of the patients have  
14 been able to quit by substituting the patch or the  
15 gum.

16 Q. Zyban is an antidepressant; correct?

17 A. Well, it's really marketed for stopping  
18 smoking, but Wellbutrin is the antidepressant, and  
19 they're the same medication.

20 Q. Do you know the reason that an  
21 antidepressant would be used to help people stop  
22 smoking?

23 MR. KEMNA: Objection.

24 A. I don't know the mechanism.

25 I think the reason it's used is clinical

1 experience, especially in the VA Hospital, found that  
2 people who took Zyban didn't smoke as much or stopped  
3 smoking.

4 Q. Have you found it to be effective?

5 A. I've only used it a few months.

6 The early results are pretty good.

7 Q. When you say pretty good, what do you  
8 mean?

9 A. I would say that more than 50 percent of  
10 the people that I've given it to are not smoking.

11 It's only a month or two, so it's hard  
12 for me to make a conclusion.

13 Q. Does nicotine effect the mood, if you  
14 know?

MR. KEMNA: Objection.

15 A. I don't know about nicotine.

16 You don't know the pharmacological  
17 effects of nicotine?

18 A. Not for that.

19 I don't know whether nicotine itself  
20 effects mood, no.

21  
22 MR. KEMNA: We've been going for a little  
23 over an hour. Is it okay to take a break?

24 MR. HOAG: Sure.

25 (Whereupon, a short break was taken.)

1 Q. (By Mr. Hoag) The people who are your  
2 patients who were smokers, when they first became your  
3 patients, did any of them exhibit any withdrawal  
4 symptoms when they attempted to stop smoking?

5 MR. KEMNA: Objection.

6 A. I can't say that any of them did, but I  
7 presume yes. If you say any, yes, there must have  
8 been some patients who had withdrawal symptoms when  
9 they stopped smoking. Feeling jittery and nervous  
10 would be the symptom I would remember.

11 Q. Did you observe any of these symptoms?

12 A. No.

13 They would complain to me.

14 Q. And would some of them say that was the  
15 reason they continued to smoke?

16 A. Yes.

17 Q. Other than feeling jittery and nervous,  
18 did any of them give any other reasons for continuing  
19 to smoke?

20 A. Well, some people say they just like it.

21 But the two common reasons are, it's  
22 relaxing or it gives me a lift, a pick up. I don't  
23 remember patients complaining that I'm down and I feel  
24 better. That's a reason that they will smoke.

25 Q. Does the Zyban relieve the jitteriness?

1 A. I don't think I have enough experience.  
2 At the end of one month, the few patients  
3 I have on Zyban feel better.

4 Q. In your opinion, does cigarette smoking  
5 cause any disease?

6 MR. KEMNA: Objection.

7 A. I don't know.

8 Q. You don't know?

9 A. I don't know.

10 Q. Do heart disease patients increase their  
11 risk of dying of heart disease by continuing to smoke?

12 MR. KEMNA: Objection.

13 I don't know that it's cause and effect.

14 The chance of death and disease  
15 progression is higher in people who continue to smoke.

16 Q. Are cigarettes addictive?

17 MR. KEMNA: Objection.

18 A. I don't know.

19 Q. Do you smoke cigarettes?

20 A. No.

21 Q. Have you ever smoked cigarettes?

22 A. No.

23 Q. Did you ever even try cigarettes?

24 A. No.

25 Q. What's the reason you never smoked

1 cigarettes?

2 A. I don't know for sure. People have said  
3 you're too cheap. Maybe I'm too cheap. I never did.

4 Q. Since you were first contacted by Shook,  
5 Hardy to work on any tobacco-related case, how many  
6 hours have you spent?

7 A. I don't know. I don't know how many  
8 hours.

9 Q. What's your best estimate of the number  
10 of hours?

11 I'll say 80, 50 to 80, something like  
12 that.

13 A. And what is your hourly fee?  
14 \$300.

15 Q. Is that hourly fee the same for a  
16 deposition as it is for reviewing literature?

17 Yes.

18 Q. Is it the same for trial testimony?

19 A. I don't know. I've never gone to trial.

20 Q. In all those times that that you've been  
21 deposed for other things other than tobacco cases,  
22 have you ever gone to trial?

23 A. Yes.

24 Q. When's the last time you testified at any  
25 trial?

- 1 A. Probably two years ago.
- 2 Q. What was your fee at that time?
- 3 A. I think it was \$300 an hour.
- 4 Q. What was that case about?
- 5 A. It was medical malpractice.
- 6 Q. Was it here in Dade County?
- 7 A. Yes.
- 8 Q. What was the name of the case?
- 9 A. I don't remember.
- 10 Q. Do you remember the names of any of the
- 11 attorneys?
- 12 A. No.
- 13 Q. What was the issue?
- 14 A. A patient who had been operated on was in
- 15 the intensive care unit and died of respiratory
- 16 arrest. They sued the doctor for improper treatment.
- 17 Q. Okay.
- 18 A. He didn't die. He had respiratory arrest
- 19 and a stroke. He had respiratory arrest, but survived
- 20 with some brain damage either due to a stroke or
- 21 something.
- 22 Q. Were you hired by the plaintiff or the
- 23 defendant?
- 24 A. The defendant.
- 25 Q. And what was the nature of your

1 testimony?

2 A. I was in defense of the doctor. I  
3 thought that the treatment he had given was standard  
4 treatment.

5 Q. What percentage of the time - when you  
6 testify as an expert witness, what percentage of the  
7 time do you testify for the defense?

8 A. Most of the time.

9 Even the cases that are referred to me, I  
10 do see plaintiff cases, but usually - I don't think  
11 I've ever had to go to court in a plaintiff case.

12 Q. When you say most of the time, how would  
13 you break that down in percentages?

14 A. It has got to be over 90 percent when I  
15 go to court. I'm not sure it isn't 100 percent when I  
16 go to court that it's in defense. That would be  
17 medical malpractice.

18 For workman's comp, I would say it's  
19 probably 80 percent defense and 20 percent plaintiff.

20 Q. What - approximately what percentage of  
21 your overall income is derived from serving as an  
22 expert witness?

23 A. It's less than ten percent.

24 Q. Now, you said that you viewed the medical  
25 record of Frosene Stevens?

1 A. Yes.

2 Q. Were you able to reach - do you have any  
3 opinions concerning the medical record of Frosene  
4 Stevens?

5 A. I don't know what opinion you mean.

6 I mean, I thought the records were good  
7 records.

8 Q. Do you have any expert opinion concerning  
9 - that you plan to provide at trial concerning the  
10 medical records of Frosene Stevens?

11 A. I think she does have coronary artery  
12 disease. I thought it was treated. I don't know the  
13 cause of her coronary disease.

14 Q. When did she first contract coronary  
15 artery disease, in your opinion?

16 A. As I say, it's a chronic progressive  
17 disease.

18 Q. The first evidence she had of heart  
19 disease was in May of 1988.

20 Q. Okay.

21 A. And at that time they thought she had  
22 cardiomyopathy, which would be a disease of the heart  
23 muscle rather than of the heart blood vessels.

24 Q. Was she a cigarette smoker in May of  
25 1988?

1 A. Yes.

2 Q. How much smoking did she do?

3 A. Based on the records, one pack a day for  
4 21 years. Other places it just says years. The best  
5 of my record here it's 21 years.

6 Q. Did she have any other risk factors for  
7 heart disease?

8 A. Yes.

9 What were those?

10 She was obese, she had an elevated serum  
11 cholesterol, and she was not on estrogen therapy, she  
12 was a 51 year old postmenopausal woman.

13 Q. Okay.

14 And she was sedentary, she also had a  
15 history of hypertension, although it's not documented  
16 in the records. There was a history, any way, of  
hypertension.

17 Q. What does sedentary or not exercising,  
18 assuming those are the same things --

19 Well, first of all, are those the same  
20 things, sedentary and not exercising?

21 A. Yes.

22 Q. By not exercising, what does that mean?

23 A. You go in the good risk group as being  
24 active. If you exercise for 30 minutes three  
25

1 different days of the week at an intensity of about 70  
2 percent of maximal effort; that means a half an hour  
3 three days a week you have to walk as fast as you can  
4 walk, or anything above that.

5 Q. Or anything equivalent to that?

6 A. Yes.

7 Q. Does that include walking up and down  
8 stairs, things like that?

9 A. Yes. But that has to be for a 30 minute  
10 period. You don't get credit for walking a flight of  
11 stairs.

12 Q. So if someone walked in the normal course  
13 of their job ten miles a day, but it took them the  
14 whole eight hours to walk the ten miles a day, would  
15 that count or would that still be sedentary?

16 MR. KEMNA: Objection.

17 A. The studies aren't usually done in that  
18 way.

19 There are studies that show that people  
20 who are active in their employment have a lower rate  
21 of heart disease or beneficial risk ratio without  
22 accumulating this half hour of vigorous exercise.

23 In other words, you said ten miles at a  
24 slower pace, that's helpful. I couldn't give you how  
25 much.

1 Q. Well, how much does it increase one's  
2 risk if they are sedentary as you define sedentary?

3 MR. KEMNA: Objection.

4 A. I don't recall any risk ratio. I don't  
5 know.

6 Q. So any risk ratio that you would come up  
7 with would just be speculation on your part?

8 MR. KEMNA: Objection.

9 A. Yes.

10 Q. Is exercise in some sense protective of  
11 heart disease?

12 A. I don't know whether it's the exercise  
13 that does it.

14 People who exercise have a lower risk, a  
15 lower ratio.

16 Q. They are at a lower risk ratio than the  
17 average person in the population?

18 A. Yes. But it may be a matter - the  
19 argument on that is like the argument on so many of  
20 these risk factors, that you've allowed the person to  
21 select his activity, it's called a self-selection, and  
22 you've immediately destroyed any randomization.

23 You don't know whether he chose to  
24 exercise because he knew he wasn't going to get heart  
25 disease or what.

1 I may not be making myself clear.

2 It's not a randomized study, therefore  
3 you can't say it's cause and effect.

4 Q. Are the epidemiological studies done on  
5 smoking and disease randomized?

6 A. No.

7 MR. KEMNA: Objection.

8 Q. Are there any epidemiological studies  
9 that are randomized?

10 MR. KEMNA: Objection.

11 A. Yes, there are. The lipid studies,  
12 cholesterol are randomized, they have been randomized.

13 Q. How does one go about randomizing an  
14 epidemiological study?

15 A. You select a population and then at  
16 random you subject half the population to whatever  
17 you're studying and the other half remains as a  
18 control.

19 Q. So for a smoker to have an  
20 epidemiological study, the fact that it's divided into  
21 smokers and nonsmokers, that still wouldn't comply  
22 with randomization, you'd have to actually do  
23 something extra to them other than just separate them  
24 into groups of smokers and nonsmokers?

25 MR. KEMNA: Objection to form.

1 A. Yes.

2 Q. And, of course, ethically you wouldn't be  
3 able to do that?

4 A. That's correct.

5 Q. So in that sense it would be impossible  
6 to do by your definition a randomized epidemiological  
7 study of smokers; is that correct?

8 MR. KEMNA: Objection.

9 I wouldn't say impossible, but you're  
10 right -- you're right, it's impossible.

11 It also turns out that it's impossible -  
12 perhaps not as impossible to do it with exercise,  
13 because you can't get the people who exercise to stop.

14 Q. Once they start exercising, you can't get  
15 them to stop?

16 A. Right.

17 Q. So are there any other risk factors that  
18 you noted in Frosene Stevens' medical records, other  
19 than obesity, elevated serum cholesterol, being a  
20 51 year old not on estrogen therapy, sedentary  
21 lifestyle, and history of hypertension?

22 A. That's all.

23 Q. Well, what is or was --

24 A. I'm sorry. I should put down family  
25 history. Her father had coronary heart disease,

1 hypertension and a stroke. The mother had coronary  
2 heart disease. She had a brother who had coronary  
3 bypass surgery at age 63, so that would be a risk  
4 factor.

5 Q. Did any of those family members smoke  
6 cigarettes?

7 A. I don't know.

8 Q. That wasn't clear from the medical  
9 records you reviewed?

10 A. I just don't remember. It may have said,  
11 but I don't remember.

12 Q. For example --

13 A. I don't believe --

14 I'm sorry.

15 I don't believe it said in the medical  
16 record. My hesitation is, she might have said in the  
17 deposition rather than the medical record. I don't  
18 remember that.

19 Q. So, for example, if either her mother or  
20 her father were smokers, were regular smokers, would  
21 that in any way alter your opinion concerning Frosene  
22 Stevens?

23 A. It wouldn't change my opinion.

24 If her mother was a smoker and had  
25 coronary artery disease, then you have to say well, at

1       least it's a modifiable risk factor. If you don't  
2       smoke, you're in a good group and she was in a bad  
3       group in terms of risk.

4           Q.     When you say she was in a bad group, are  
5       you talking about Frosene's mother or Frosene herself  
6       or both?

7           A.     Frosene's mother.

8                 You asked me, I believe, does it change  
9       my opinion?

10                It doesn't change my opinion.

11                If Frosene's mother was a smoker, one of  
12       Frosene's mother's risk factors was modifiable.

13                If that could be deducted from Frosene as  
14       a risk factor, then it it makes the family history or  
15       her hereditary risk less meaningful.

16           Q.     You said obesity. What was her level of  
17       obesity at the time you looked at these medical  
18       records?

19           A.     I didn't write it down.

20           Q.     Do you know whether she was more than  
21       30 percent over her ideal weight?

22           A.     No, I don't.

23           Q.     What was her serum cholesterol level?

24           A.     The one I wrote down was 341. She had  
25       several measurements. She had a cholesterol that at

1 one time was over 300.

2 Q. What was the HDL and LDL ratio?

3 A. I don't remember. I'm not sure it was  
4 done.

5 Q. If someone has an LDL level of 65, does  
6 that total of 341 become less meaningful?

7 MR. KEMNA: Objection.

8 A. I think what you postulate isn't  
9 possible.

10 It has to somehow add up to 365.

11 The HDL and the LDL - in other words, we  
12 couldn't get up to 300 if her LDL is too low.

13 Maybe I'm saying it wrong. That's quite  
14 possible.

15 Which of the two is the one that has some  
16 protective qualities?

17 MR. KEMNA: Objection.

18 A. The HDL.

19 Q. Okay.

20 A. But I think the way you were trying to  
21 say the question was, if her cholesterol was 341 and a  
22 large part of it was HDL, would that make a  
23 difference.

24 I'm saying yes.

25 One way to measure that risk is to divide

1 the total cholesterol by the HDL, and you'd like the  
2 ratio to be under four and a half.

3 I don't recall seeing that in her record.

4 Q. Whether it was or wasn't?

5 A. I don't know.

6 Q. So if it was under 4.5, then the serum  
7 cholesterol level would not be a risk factor for her;  
8 is that correct?

9 MR. KEMNA: Objection.

10 A. I believe it would still be a risk  
factor, but not as severe.

11 Q. Is it just a belief or do you know that?

12 I know that.

13 What's not known is which lipid  
14 measurement, if you had to pick one, would be the best  
15 one.

16 I think it's clear that the more lipid  
17 measurements you make, the better handle you have on  
18 it.

19 You're asking me is the LDL, the HDL or  
20 the total the most important?

21 I have to say all of them are important.

22 Since you have the option of doing all of  
23 them, there's no reason to say which one is the single  
24 best one.  
25

1 Q. Have there been some studies that  
2 indicate that the number that really matters is the  
3 HDL number rather than the total number?

4 A. Not to the exclusion of the total.

5 If the total is normal, then the HDL is  
6 the most important.

7 And there are people who have low HDLs  
8 with everything else being normal with coronary  
9 disease, so in them, of course, it's the most  
10 important. But as a screening measure you really need  
11 all three.

12 Q. Okay. As far as the risk, the increased  
13 risk caused by the elevated serum cholesterol level,  
14 you don't know what that is?

15 MR. KEMNA: Objection.

16 A. The figures I gave you had that one  
17 percent reduction in total cholesterol causes a two  
18 percent reduction in the risk of heart disease.

19 Q. I guess what I'm getting at, you have to  
20 know her HDL level in order to be able to accurately  
21 assess the level of risk as far as the cholesterol  
22 level; is that correct?

23 MR. KEMNA: Objection.

24 A. It would help you.

25 You can say that a level of serum

1 cholesterol of 341 or anything over 300 is too high.  
2 That's a risk of heart disease. If you lower it by  
3 one percent, you'll presumably get a two percent  
4 rededuction in that risk.

5 Q. When you say - that was one total or  
6 cumulative cholesterol level that you looked at.

7 How many different cholesterol levels had  
8 been taken as evidenced in her medical record?

9 I can't tell you. I don't know.

10 Were they all as high as 341?

11 A. No.

12 Probably that was the first one, it was  
13 probably the highest one. She was put on treatment  
14 with medication to lower her serum cholesterol.

15 I think that all her levels were probably  
16 over 200, but I didn't write them down and I don't  
remember them.

17 Q. Did the medication help in lowering her  
18 cholesterol level?

19 A. Yes.

20 Q. Once her cholesterol level was lowered,  
21 did that eliminate the cholesterol level as a risk  
22 factor?  
23

24 MR. KEMNA: Objection.

25 A. It doesn't eliminate it. It reduces it.

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1 As I say, I don't believe her's was ever  
2 down to a goal level, which would be less than 200  
3 total.

4 In her case, because she has coronary  
5 disease, you'd like the LDL to be under 130 and  
6 preferably under 100. I don't think she reached those  
7 levels. The medication was helpful.

8 Q. At the time she was diagnosed with the  
9 disease she was, based on your testimony and your  
10 review, she was 51 years old and not on estrogen  
therapy

11 How does that increase her risk for heart  
12 disease?

13 MR. KEMNA: Objection.

14 A. I can't give you the relative risk, but  
15 it increases the risk.

16 Q. Is it more than two or do you know?

17 A. I don't know.

18 Q. And was she placed on estrogen therapy?

19 A. I don't know if she was permanently on  
20 it. At one time she was given estrogen. I can't give  
21 you the dates of when it was started and whether she  
22 continued to take it.

23 Q. Would that decrease the risk factor for  
24 not having estrogen therapy, to be placed on it?  
25

1 MR. KEMNA: Objection.

2 A. Yes. Replacement estrogen therapy does  
3 reduce the risk.

4 Q. So to the extent that she was placed on  
5 it, that would have reduced her risk in that regard;  
6 is that correct?

7 A. Yes.

8 Q. And when you said sedentary, what were  
9 you basing that on?

10 A. I think her doctor advised her to  
11 exercise, so I'm making the presumption that she  
12 wasn't exercising prior.

13 Q. So your definition of sedentary then is  
14 anyone who does less than three days per week of  
15 rigorous exercise for 30 minutes each of those three  
16 days; is that correct?

17 MR. KEMNA: Objection.

18 A. Yes.

19 MR. DODDS: Asked and answered.

20 Q. What percentage of the population would  
21 fall into the category based on your definition of  
22 sedentary of being sedentary?

23 A. I don't know.

24 Q. Would it be the majority of the  
25 population?

1 MR. KEMNA: Objection.

2 A. Again, I don't know.

3 I'm sure it depends on age and gender. I  
4 don't think you could give a figure for the  
5 population. If you select a group, you might. But I  
6 don't know the answer.

7 Q. Well, for example, hypothetically, if  
8 90 percent of the population by your definition is  
9 sedentary, would that change the relative  
10 meaningfulness of labeling sedentary as a risk factor?

11 MR. KEMNA: Objection.

12 A. I don't think it would change it, no.

13 History of hypertension, what was her  
14 history of hypertension?

15 A. Well, on admission and in the hospital  
16 they thought that she had hypertension. I have no  
17 history that she was ever treated prior to this  
18 admission for hypertension. The statement that I  
19 wrote in my notes are that she has a history of labile  
20 blood pressure.

21 Q. That means high?

22 A. That means high and low; sometimes high,  
23 sometimes low.

24 Q. And you don't know from reading the  
25 records whether or not she was placed on any kind of

1 medication to regulate --

2 A. She was when she came to the hospital.  
3 Her blood pressure was elevated 160/90, and she was  
4 given antihypertensive medication.

5 But prior to the hospitalization it was  
6 only this history of labile hypertension and no  
7 treatment that I'm aware of.

8 Q. Did the antihypertensive medication work?  
9 A. Yes.

10 Q. What did it bring it down to?

11 A. I have to say normal levels, but I didn't  
12 write the actual figures.

13 Q. If she stayed on that medication, if she  
14 had stayed on that medication since then, would that  
15 now eliminate that as a risk factor for her in the  
16 future?

17 A. Doesn't eliminate it, but it helps.

18 It's hard to prove in hypertensive  
19 patients that normalizing the blood pressure with  
20 medication reduces their risk of heart attacks. It  
21 definitely reduces strokes, but it's hard to show -  
22 when I say hard to show, it means some studies have  
23 shown improvement and some studies have failed to show  
24 improvement in the rate of heart attacks.

25 Q. And did she continue to smoke cigarettes?

1 A. I don't know. That is her statement  
2 saying that she stopped smoking, and there are other  
3 statements saying she didn't stop.

4 Q. Hypothetically if there was a patient who  
5 had this same exact disease, who was a current smoker  
6 at the time they were diagnosed, and had been smoking  
7 two packs of cigarettes a day for 20 years, who had  
8 none of the other known risk factors, would you be  
9 able to reach a conclusion as to whether or not  
10 smoking was the cause of their heart disease?

MR. KEMNA: Objection to form.

12 A. No.

13 Q. So the risk factors don't really make any  
14 difference to you as far as being able to diagnose  
15 whether or not smoking was the cause; is that correct?

MR. KEMNA: Objection.

17 Q. The cause of the disease?

18 MR. KEMNA: Objection.

19 A. No. The risk factors make a big  
20 difference to me in diagnosing the heart disease and  
21 treating the patient.

22 I still don't know what caused the heart  
23 attack or the heart disease.

24 A lot of patients have no risk factors at  
25 all and they get heart attacks and heart disease

1 without any risk factors.

2 Q. So are there any circumstances under  
3 which you could foresee being able to state that  
4 someone's - someone who contracted heart disease  
5 contracted the heart disease as a result of smoking  
6 cigarettes?

7 MR. KEMNA: Objection.

8 A. No.

9 Q. How about as to any of the other risk  
10 factors you named, same question?

11 A. No. That is, I believe the question is  
12 saying do I envision a way of showing that one of the  
13 ~~most~~ factors caused the heart disease in a particular  
14 ~~patients~~. My answer is no.

15 Q. Would you be able to - is there any  
16 circumstances under which you could - you would be  
17 able to testify that it was more likely than not that  
18 smoking caused an individual patient's heart disease?

19 MR. KEMNA: Objection.

20 A. No.

21 Q. Are there any circumstances - given the  
22 fact -- Scratch that.

23 Hypothetically, given the fact that a  
24 person is a current smoker at the time they're  
25 diagnosed with heart disease, are there any factors -

1 any situation that you could envision where you would  
2 be able to say that it is more likely than not that  
3 the heart disease was not caused by smoking?

4 MR. KEMNA: Objection.

5 A. No. I don't know the cause of the heart  
6 disease so I wouldn't be able to say it was or was  
7 not.

8 (Whereupon, a short break was taken.)

9 (By Mr. Hoag) Just a couple more  
10 questions.

11 Prior to working on tobacco-related cases  
12 for Shook, Hardy and Bacon, had you ever done any  
13 other work for Shook, Hardy and Bacon?

14 No.

15 Had you ever done any other work for any  
16 of the law firms that you are aware represent tobacco  
17 companies?

18 A. I don't believe so. I mean, unless they  
19 had something to do with a medical malpractice case.  
20 I never had anything to do with anything except  
21 workman's comp and medical malpractice.

22 Q. And were any of the worker's comp cases  
23 in any way related to tobacco smoking?

24 A. I don't believe so.

25 Q. And other than this deposition today,

1 have you ever given a deposition that was in any way  
2 related to cigarette smoking?

3 A. No.

4 Q. Do you know whether anyone recommended  
5 you as a possible expert witness in this case or any  
6 other tobacco-related case?

7 A. Somebody must have recommended me, but I  
8 don't know who. I don't remember how it - when they  
9 came to my office, a group of attorneys, they said  
10 somebody had recommended me, but I don't remember who.

11 Q. They told you somebody, but you don't  
12 remember who?

13 A. That's my memory.

14 When you say have I ever been in a  
15 deposition, yes. If it has to do with heart disease  
16 and if somebody said isn't tobacco a risk factor, I  
would have to say it was a risk factor.

17 It was never specifically related to  
18 tobacco as having to do with usually workman's comp,  
19 with extra exertion or exposure to an injury.

20 Q. Do you keep a list of the cases that  
21 you've served as an expert in?

22 A. No.

23 Q. Would you have any of the names of any of  
24 the cases where you've been an expert?  
25

1 A. For tobacco?

2 Q. I'm talking about even the worker's comp.  
3 or the medical malpractice cases?

4 A. No.

5 I mean, I know my office has the list of  
6 attorneys that send us cases, because that's who we  
7 bill. I don't remember any of them by name.

8 Q. You have a list of attorneys who  
9 regularly refer you --

10 A. It's not a separate list.

11 If I say - if I ask the girls could you  
12 look at the bills for the last year to attorneys  
13 firms, they could name the firms.

14 Q. Would that also include the names of the  
15 cases or not?

16 A. I don't believe so. Because in the  
17 tobacco billing we looked and it doesn't have the name  
18 of the case, it just says medical record review.

19 Q. Do you remember the names of any of the  
20 cases that you have - were you were serving as an  
21 expert witness?

22 MR. KEMNA: Objection.

23 To the extent that that calls for any  
24 response dealing with any role Dr. Gilmore may  
25 have played as a pure consultant in cases where

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# Evaluating Coronary Heart Disease Risk

## Tiles in the Mosaic

Jeffrey M. Hoeg, MD

### SELECTED CASE

An asymptomatic 34-year-old white man was referred to the Lipid Clinic of the National Heart, Lung, and Blood Institute for atherosclerotic cardiovascular disease risk assessment. His father died at the age of 39 years of a myocardial infarction, and his 2 paternal uncles developed symptomatic coronary artery disease by the age of 40 years. The search for conventional cardiovascular disease risk factors was unrevealing. The patient exercised regularly and had never smoked tobacco products. Physical examination revealed a normotensive man within 3% of his ideal body weight. His fasting concentrations of blood glucose (5.32 mmol/L [95 mg/dL]), low-density lipoprotein cholesterol (LDL-C) (1.76 mmol/L [68 mg/dL]), and high-density lipoprotein cholesterol (HDL-C) (1.06 mmol/L [41 mg/dL]) were all within normal limits. However, his fasting plasma triglyceride concentration was increased to 6.4 mmol/L (588 mg/dL) as was his apolipoprotein B concentration at 3.90 mmol/L (150 mg/dL) (normal range, 1.94-3.33 mmol/L [75-129 mg/dL]). The apolipoprotein A-I concentration was low (2.74 mmol/L [105 mg/dL]) (normal range, 2.79-4.42 mmol/L [108-171 mg/dL]), the lipoprotein (a) [Lp(a)] concentration was 0.05 mmol/L (2 mg/dL) (desirable <0.26 mmol/L [ $<10$  mg/dL]), and his plasma homocysteine level was 15.0  $\mu$ mol/L (normal range, 4-17  $\mu$ mol/L). Exercise treadmill and thallium testing did not reveal inducible myocardial ischemia, but the total calcium score of the coronary arteries by electron beam tomography (ultrafast computed tomography) was 147 (normal range, 9-46).

### DISCUSSION

Coronary artery disease is endemic in the developed world. This process begins in childhood<sup>1</sup> and leads to heart disease, the most common cause of death in the

United States.<sup>2</sup> However, there are some individuals who are at an even greater risk than the general population for developing symptomatic coronary artery disease. The identification of those individuals and the application of techniques to directly interfere with their atherogenic disease process is the central goal of preventive cardiology. Although the "risk factor" concept now permeates medical practice, the present case illustrates that the currently established risk factors do not fully describe a particular individual's propensity for developing symptomatic cardiovascular disease. Therefore, the search for new cardiovascular disease risk factors that would have predictive and therapeutic utility continues.

A family history of premature and aggressive cardiovascular disease is the most remarkable feature in the present case. The development of ischemic heart disease symptoms before the age of 40 years in the men on the paternal side of this patient's family indicates the possibility of a genetic predisposition to atherogenesis. In the absence of the established cardiovascular disease risk factors of obesity, diabetes mellitus, hypertension, and cigarette smoking, other genetic causes for enhanced susceptibility must be considered. The presence of substantial calcification detected by electron beam tomography in this patient's coronary arteries establishes that this patient not only has a positive family history for heart disease, but also a rampant atherogenic process that is independent of the conventionally recognized cardiovascular disease risk factors. What other risk factors can account for disease in this patient? This review will point to new concepts and clinical tools that may be useful to detect and arrest atherogenesis long before it becomes clinically manifest.

### History of Cardiovascular Disease Risk Factors

The concept of "risk factors" is a relatively recent one. Early in this century, unique infectious organisms were established to cause specific diseases. The parallel with genetic causes for disease were implicit in the "one gene-one enzyme" of

Beadle and Tatum<sup>3</sup> and bolstered the view that defects in specific genes would lead to unique inborn errors of metabolism.<sup>4</sup> With the initiation of the Framingham Heart Study in 1948, the expectation was that causal relationships would be observed among candidate causes for cardiovascular disease. "The cause" of coronary atherosclerosis would be discovered. However, it became apparent through the first decade of the study in Framingham that sole-cause etiologies were not emerging from the study. Instead, a number of different parameters were correlated with the development of cardiovascular disease. The first use of the term "factors of risk" in 1961 was in the context that "no single essential factor has been identified" to cause coronary heart disease.<sup>5</sup> Therefore, these characteristics are like the tiles that are used to make a mosaic. Isolated, the color and consistency of the individual tile does not provide substantial insight, but taken together, a constellation of tiles defines the picture for both the mosaic and for the propensity to develop cardiovascular disease. This clearer definition of risk is useful in the treatment of an individual patient, such as the present case, as well as in applying the principles of public health to reduce cardiovascular disease risk in the general population.

### Conventional Cardiovascular Risk Factors

The now-familiar cardiovascular disease risk factors are summarized in Table 1. The term risk factor was not intended to imply causality. The term was established for parameters that would help to identify individuals with increased cardiovascular disease risk. Some of the risk factors including age, sex, and family history cannot be modified. However, these characteristics have been used as a guide to determine the intensity of the therapy directed to those elements which may play a causal role in atherogenesis and that can be modified. The Adult Treat-

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Table 1.—Established Cardiovascular Disease Risk Factors

Nonmodifiable factors
Age
Sex
Family history
Modifiable factors
Cigarette smoking
Obesity
Hypertension
Physical inactivity
Diabetes mellitus
Cholesterol
Elevated low-density lipoprotein cholesterol
Reduced high-density lipoprotein cholesterol

ment Panel of the National Heart, Lung, and Blood Institute has used the established risk factors to determine the goals of therapy to lower the concentrations of atherogenic LDL.<sup>6</sup> In addition to reducing total cholesterol and LDL-C concentrations, the treatment of hypertension and obesity have entered into the mainstream of clinical practice. Moreover, patients are admonished to alter their lifestyles, to discontinue cigarette smoking, and to increase their daily activity to at least 30 minutes on most days of the week. Therefore, the concept of risk factors has evolved from establishing statistical associations to directly modifying factors that modulate the atherogenic process in the arterial wall.

The modification of cardiovascular risk is most clearly established in the reduction of total cholesterol and LDL-C concentrations. The treatment of patients with elevated concentrations of total cholesterol and LDL-C has been shown to reduce the incidence of myocardial infarction,<sup>7,8</sup> cerebrovascular events, cardiovascular death, and all-cause mortality as both "secondary" intervention<sup>9,10</sup> and as "primary" intervention.<sup>11</sup> The treatment of the underlying pathophysiologic process in the artery is the same regardless of whether the patient has or has not already suffered a cardiovascular disease event (secondary or primary intervention). Instead, we are treating the atherosclerosis in patients who have or have not yet experienced a cardiovascular disease event.

#### The Detection of Cardiovascular Disease

The case that was initially described in this article illustrates that the conventional cardiovascular disease risk factors do not always lead to therapies that can prevent cardiovascular disease. The only conventional risk factor that was present was that of a strongly positive family history. Does this patient have a malignant underlying atherogenic process? The thallium and exercise stress tests did not indicate the presence of flow-obstructing coronary artery disease lesions, but coro-

Table 2.—Methods to Detect Atherosclerosis in Men

Technique	Advantages	Disadvantages
Angiography	Established "gold standard," directs interventional therapy	Invasive, expensive, underestimates extent of atherosclerosis
Intravascular ultrasound	Direct visualization of arterial wall, therapeutic implications for angioplasty	Invasive, expensive, not widely available
Transesophageal echocardiography	Detection and quantitation of aortic atherosclerosis, high resolution	Moderately invasive, expensive, not widely available
Carotid ultrasound	Noninvasive, quantitates atheroma, inexpensive	Difficult to standardize
Magnetic resonance imaging	Noninvasive, direct assessment of arterial wall, both structural and flow determination	Not yet linked to clinical decisions, protocols still experimental, expensive
Electron beam tomography	Noninvasive, fast, inexpensive, correlates with cardiovascular events	Only detects calcific atherosclerosis, not yet linked to clinical decisions

nary atherosclerosis generally proceeds diffusely<sup>12</sup> and need not result in exercise-induced ischemia. Therefore, as exemplified by this case, conventional cardiovascular risk assessment often does not provide a full picture of a given patient's underlying disease process.

The initial search for risk factors used either the onset of cardiovascular disease symptoms or cardiovascular disease death as the reference correlates. However, human atherosclerosis is an indolent, progressive, and complex process. A classification has recently been devised characterizing 6 types of vascular lesions that have pathophysiologic relevance.<sup>14</sup> New methods are under development to provide a direct assessment of the progression of atherogenesis at the arterial wall prior to the onset of either symptoms or sudden death (Table 2). Angiography has long represented the definitive assessment of coronary artery atherosclerosis; however, detection of flow-limiting lesions may not entirely reflect the risk that a given patient may have for a cardiovascular disease event. In fact, the characteristics of the plaque that subsequently ruptures to produce acute coronary thrombosis cannot be predicted by coronary angiography.<sup>14,15</sup> Therefore, other methods are being used to assess the extent, characteristics, and severity of atherosclerosis that cannot be determined by the "lumenogram" generated by coronary angiography.

Intravascular ultrasound has been developed to evaluate the characteristics of the walls of coronary arteries and has been particularly useful in the setting of angioplasty and the placement of stents.<sup>17</sup> Since the ultrasound probe is at the tip of the catheter used routinely for angiography, it is possible to assess the extent of luminal narrowing as well as detect intracoronary artery mural calcification. In addition, it is now possible to determine the extent of plaque within the coronary artery using intravascular ultrasound.<sup>18</sup> Although this technique is not widely available, it should prove useful in determining the impact of specific interventions on the extent of coronary artery atherosclerosis.

In addition to direct assessment of the coronary arteries, the evaluation of other vascular beds may have clinical utility because of the diffuse nature of atherosclerosis. The risk for cerebral, myocardial, and peripheral vascular disease events has been associated with the severity of aortic atheromatous plaque determined by transesophageal echocardiography.<sup>19</sup> Assessment of carotid artery atherosclerosis by ultrasound correlated with the risk for experiencing a cardiovascular event as well as the efficacy of cholesterol reduction in reducing the risk for a cardiovascular disease event.<sup>20</sup> These findings suggest that non-coronary artery vascular beds may be central to vascular events as well as provide a means of more accurately defining patients prone to cardiovascular morbidity and mortality.

In addition to evaluating the aorta and the carotids, new noninvasive methods are under development to directly investigate the coronary artery wall in vivo. Magnetic resonance imaging of the coronary arteries can give both structural as well as coronary blood flow assessment.<sup>21,22</sup> The information not only correlates with the conventional coronary angiography, but the quantitation and characterization of the arterial plaque itself may become useful in making routine clinical decisions that complement the information derived from coronary arteriography.

Another technique that may prove useful in assessing a patient's cardiovascular disease risk is electron beam tomography (formerly ultrafast computed tomography). This method detects and quantifies the calcification present in the atherosclerotic plaque.<sup>23</sup> Calcification has long been recognized in complex atheromas present in sclerotic vessels, and the first in vivo detection of calcific atherosclerosis by fluoroscopy was reported 70 years ago.<sup>24</sup> The calcification process represents the elaboration of gene products by the differentiated monocyte-macrophage in the arterial wall<sup>25</sup> and the process resembles nascent bone formation.<sup>26</sup> By gating the electron beam to the electrocardiogram, a computed image can be generated in

the moving epicardial coronary arteries. The electron beam tomogram can detect both flow-limiting stenotic lesions as well as calcific atherosclerotic plaque that is present in regions not discernibly abnormal by coronary angiography.<sup>24-27</sup> Recent studies indicate that detection and quantitation of calcific lesions in the coronary arteries is very informative. First, there is a high correlation of calcification with segmental coronary artery atherosclerosis defined histopathologically.<sup>28</sup> Second, for severity of calcification, the area under the receiver operating characteristic curve ranges from 0.712 to 0.857 to predict the extent of luminal area narrowing observed at autopsy. In addition, it compares favorably with the prediction of severity of coronary artery disease by treadmill and thallium stress testing in patients undergoing coronary angiography.<sup>29</sup> Finally, recent data from a prospective study<sup>30,31</sup> of asymptomatic subjects indicate that electron beam tomography may be highly effective in predicting cardiovascular disease events.<sup>30</sup> The area under the receiver operating characteristic curve for this predictive power was a remarkable 0.91. The current patient had a coronary artery calcification score of 147. This indicates that this patient's risk for developing a cardiovascular disease event is increased 25 times with a sensitivity and specificity of 0.89 and 0.77, respectively.<sup>30</sup> Therefore, this patient's electron beam tomogram indicates that he has most likely inherited the gene(s) that lead to accelerated calcific atherosclerosis from the paternal side of his family.

#### New and Proposed Cardiovascular Disease Risk Factors

The search for additional risk factors continues, since nearly 25% of patients with premature cardiovascular disease do not have one of the established risk factors. In addition, the underlying cause of enhanced atherogenesis susceptibility, as exemplified in the current case report, is not established in many individuals with a strong family history of premature symptomatic cardiovascular disease.

Our society is inundated daily in the lay press with a myriad of suggestions for additional risk factors. These range from coffee and garlic consumption to the intake of a variety of macronutrients and micronutrients such as *trans*-fatty acids, folate, and vitamin E. The broad public interest reflects the explosion of novel parameters published in the biomedical research literature which have biologically plausible influences on atherogenesis. As with many multifactorial disease processes, the development of atherosclerosis as well as symptomatic cardiovascular

disease is likely to be influenced by a convergence of many different determinants. However, establishing the validity of a proposed risk factor requires careful epidemiologic investigation. It is left to the well-designed clinical trial to finally assess whether the selective modification of a specific risk factor can prevent disease.

The established cardiovascular disease risk factors have all been validated by epidemiologic investigation (Table 1). However, only the treatment of high LDL-C concentrations<sup>4-10</sup> and hypertension<sup>11-23</sup> have been established by clinical trials to reduce cardiovascular morbidity and mortality. Of the more than 100 potential additional cardiovascular disease risk factors that have been proposed, I have selected 17 that are particularly promising and have therapeutic implications (Table 3). The present case is that of a man, however, and it should be noted that a great deal remains to be accomplished in evaluating risk factors and their therapeutic implications in women. All of these risk factors reflect concentrations or activities that are found within blood. The discovery of new risk factors will undoubtedly emerge from the ongoing investigation of cellular gene expression within the arterial wall.

Plasma total cholesterol and LDL-C concentrations do not fully represent the impact that the plasma lipoproteins have on the atherogenic process and the initiation of cardiovascular disease events. Several lipoprotein particle subspecies characterized by their apolipoprotein composition, their size, and their susceptibility to oxidation appear to be proatherogenic (Table 3). Triglyceride-rich apolipoprotein B-100 particles associated with apolipoprotein C-III, apolipoprotein E-2 and E-4 isoforms, and small, dense, cholesterol-poor LDL particles may be particularly atherogenic. The current patient manifests high fasting triglyceride concentrations as well as elevated levels of apolipoprotein B. The increase in the triglyceride-rich apolipoprotein B is observed in type III hyperlipoproteinemia (dysbetalipoproteinemia) and reflects a cholesterol-poor, yet proatherogenic lipoprotein particle. Since a substantial fraction of patients presenting with a myocardial infarction before the age of 60 years have increased plasma concentrations of these particles in the fasting state,<sup>34</sup> it has been suggested that the determination of the concentrations of apolipoprotein B<sup>35</sup> or subspecies of apolipoprotein B particles<sup>36</sup> in hypertriglyceridemic patients may be useful in assessing cardiovascular disease risk.

There are many other proatherogenic factors that can either lead to endothelial dysfunction and death or enhance cellular proliferation within the atheroma. The re-

Table 3.—Proposed Cardiovascular Disease Risk Factors

Proatherogenic
Homocysteine
Lipoprotein particle oxidation
Hyperviscosity
Lipoprotein particle subspecies
Apolipoprotein E isoforms
Cholesteryl ester transfer protein
Prothrombotic
Plasminogen
Fibrinogen
Factor VII
Plasminogen activator inhibitor 1
Lipoprotein (a)
Antiatherogenic
Apolipoprotein A-I
Lecithin:cholesterol acyl transferase
Hepatic lipase
Low-density lipoprotein receptor
Very low-density lipoprotein receptor
Apolipoprotein E

sponse to arterial injury elicits a cascade of interrelated processes directed toward healing the injury.<sup>37</sup> Homocysteine<sup>38</sup> and oxidized lipoproteins<sup>39</sup> are toxic to endothelial cells, and there is evidence that some patients may be more likely to have high concentrations of these substances. Alternatively, high concentrations of insulin may stimulate cellular proliferation and be detrimental by increasing the exuberance of the response to the injury.

Cardiovascular disease is due to a variety of biological processes including acute thrombosis. There are a number of factors involved in the physiology of clot formation that are risk factor candidates. The initial activation of plasminogen that leads to cleavage of fibrinogen to generate fibrin is a complex process involving an array of plasma proteins and cellular receptors. High concentrations of fibrinogen, which is increased in cigarette smokers, is correlated with the incidence of myocardial infarction. Similarly, plasminogen concentrations, factor VII concentrations, and plasminogen activator inhibitor 1 (PAI-1) levels also correlate with the risk for developing an ischemic event. Since PAI-1 associates with triglyceride-rich lipoproteins, this factor and Lp(a), which contains structural motifs resembling plasminogen, link the plasma lipoproteins with thrombosis. Although the present patient had a low Lp(a) concentration, the sequestration of PAI-1 by his triglyceride-rich lipoprotein may predispose him to thrombosis.

In contrast, antiatherogenic risk factors may attenuate atherosclerotic risk. Candidates for antiatherogenic factors have been generated using transgenic animal models. Subspecies of HDL particles containing apolipoprotein A-I without apolipoprotein A-II, termed LpA-I particles, appear to be especially antiatherogenic. Several enzymes, including hepatic lipase and lecithin:cholesterol acyl transferase (LCAT), modulate HDL metabolism, and LCAT has recently been shown to pre-

vent atherosclerosis in a transgenic animal model.<sup>40</sup> In addition, overexpression of the genes affecting clearance of atherogenic lipoprotein particles, including the LDL receptor, the very low-density lipoprotein receptor, and apolipoprotein E-3, might even be termed "therapeutic" risk factors.<sup>41,42</sup>

In the present case, the presence of substantial calcific coronary artery atherosclerosis defined by electron beam tomography led to the search for other possibilities other than the conventionally accepted cardiovascular disease risk factors. The concentrations of homocysteine and Lp(a) on this patient were normal. The blood concentrations of these 2 substances can be reduced by folate and niacin/

LDL apheresis, respectively. Ongoing and future clinical trials are required to determine the efficacy of the reduction of homocysteine and Lp(a) on reducing cardiovascular risk. The "normal" plasma LDL-C concentration was in the context of markedly increased concentrations of triglyceride-rich apolipoprotein B concentrations. Patients with this lipoprotein phenotype experienced a reduced incidence of cardiovascular sequelae with the use of the fibric acid derivative gemfibrozil.<sup>4</sup> Alternatively, niacin, which can reduce the concentrations of these particles as well as raise HDL-C, has been demonstrated to reduce cardiovascular disease sequelae and all-cause mortality in patients with prior myocardial infarction.<sup>43</sup> This patient

was treated by gradually increasing the niacin dosage to 500 mg of crystalline niacin 3 times a day with meals. This reduced his fasting triglyceride concentrations from 6.64 mmol/L (588 mg/dL) to 3.22 mmol/L (285 mg/dL) and his apolipoprotein B concentrations from 3.90 to 2.78 mmol/L (151 to 107 mg/dL).

In summary, the concept of cardiovascular risk factors is firmly established in routine clinical practice. With the advent of more sensitive and specific screening methods, atherosclerosis detection and risk factor assessment will become more refined. These tools coupled with the results from ongoing clinical trials will permit ever more effective therapy to prevent cardiovascular disease.

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Account #: 18589

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Ref#	Date	Patient	Dr	Procedure	Adj Chgs	Receipts
Unapplied Credits :						0.00
	03/07/97		1	99199 -MEDICAL RECORD REVIE	600.00	0.00
	03/17/97		1	99199 -MEDICAL RECORD REVIE	600.00	0.00
	05/16/97		1	99199 -MEDICAL RECORD REVIE	300.00	0.00
	11/11/97		1	99199 -MEDICAL RECORD REVIE	300.00	0.00
TOTALS : BALANCE :					1800.00	0.00

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VOLUME 336

APRIL 3, 1997

NUMBER 14



## INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN

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### ABSTRACT

**Background** Inflammation may be important in the pathogenesis of atherothrombosis. We studied whether inflammation increases the risk of a first thrombotic event and whether treatment with aspirin decreases the risk.

**Methods** We measured plasma C-reactive protein, a marker for systemic inflammation, in 543 apparently healthy men participating in the Physicians' Health Study in whom myocardial infarction, stroke, or venous thrombosis subsequently developed, and in 543 study participants who did not report vascular disease during a follow-up period exceeding eight years. Subjects were randomly assigned to receive aspirin or placebo at the beginning of the trial.

**Results** Base-line plasma C-reactive protein concentrations were higher among men who went on to have myocardial infarction (1.54 vs. 1.13 mg per liter,  $P < 0.001$ ) or ischemic stroke (1.38 vs. 1.13 mg per liter,  $P = 0.02$ ), but not venous thrombosis (1.26 vs. 1.13 mg per liter,  $P = 0.34$ ), than among men without vascular events. The men in the quartile with the highest C-reactive protein values had three times the risk of myocardial infarction (relative risk, 2.9;  $P < 0.001$ ) and two times the risk of ischemic stroke (relative risk, 1.9;  $P = 0.02$ ) of the men in the lowest quartile. Risks were stable over long periods, were not modified by smoking, and were independent of other lipid-related and non-lipid-related risk factors. The use of aspirin was associated with significant reductions in the risk of myocardial infarction (55.7 percent reduction,  $P = 0.02$ ) among men in the highest quartile but with only small, nonsignificant reductions among those in the lowest quartile (13.9 percent,  $P = 0.77$ ).

**Conclusions** The base-line plasma concentration of C-reactive protein predicts the risk of future myocardial infarction and stroke. Moreover, the reduction associated with the use of aspirin in the risk of a first myocardial infarction appears to be directly related to the level of C-reactive protein, raising the possibility that antiinflammatory agents may have clinical benefits in preventing cardiovascular disease. (N Engl J Med 1997;336:973-9.)

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**T**HROMBUS formation is the proximate cause of myocardial infarction, but atherosclerosis, the chief underlying cause, is a chronic disease that progresses over decades of life.<sup>1</sup> Laboratory and pathological data support the idea that inflammation has a role in both the initiation and the progression of atherosclerosis, and antiinflammatory agents may have a role in the prevention of cardiovascular disease.<sup>2-6</sup> However, there are few data to indicate whether inflammation increases the risk of first myocardial infarction, stroke, and venous thrombosis or whether antiinflammatory therapy decreases that risk.

C-reactive protein is an acute-phase reactant that is a marker for underlying systemic inflammation. Elevated plasma concentrations of C-reactive protein have been reported in patients with acute ischemia<sup>6</sup> or myocardial infarction<sup>7,8</sup> and have been found to predict recurrent ischemia among those hospitalized with unstable angina.<sup>9</sup> C-reactive protein is also associated with a risk of myocardial infarction among patients with angina pectoris<sup>10</sup> and with a risk of fatal coronary disease among smokers with multiple risk factors for atherosclerosis.<sup>11</sup> However, since concentrations of C-reactive protein and other acute-phase reactants increase after acute ischemia<sup>6</sup> and are directly related to cigarette smoking,<sup>11,12</sup> it has been uncertain whether associations observed in previous studies of acutely ill patients<sup>9</sup> or high-risk popula-

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tions<sup>10,11</sup> are causal or are due to short-term inflammatory changes or to interrelations with other risk factors, in particular smoking and hyperlipidemia.

To address these issues, we measured base-line plasma C-reactive protein concentrations in 1086 apparently healthy men participating in the Physicians' Health Study<sup>12,13</sup>; myocardial infarction, stroke, or venous thrombosis subsequently developed in 543. We hypothesized a priori that levels of C-reactive protein would predict the risk of myocardial infarction and stroke but not of venous thrombosis — an occlusive vascular disease generally not associated with chronic atherosclerosis. After providing base-line blood samples, study participants were randomly assigned to receive aspirin or placebo. Thus, we had the unique opportunity to evaluate directly whether aspirin, an agent with both antiplatelet and anti-inflammatory properties, might modify any relation between C-reactive protein and the risk of first myocardial infarction.

## METHODS

### Study Population and Collection of Plasma Samples

The Physicians' Health Study was a randomized, double-blind, placebo-controlled two-by-two factorial trial of aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer. A total of 22,071 male physicians 40 to 84 years of age in 1982, with no history of myocardial infarction, stroke, transient ischemic attack, or cancer, were assigned to one of four treatment groups: aspirin on alternate days (Bufferin, provided by Bristol-Myers), 50 mg of beta carotene on alternate days (Eurotin, provided by BASF Corporation), both, or neither. The aspirin component of the study was terminated early, on January 26, 1988, primarily because of a statistically extreme 44 percent reduction in the risk of a first infarction in the aspirin group.<sup>12</sup> The beta carotene component continued until the study's scheduled termination on December 31, 1995.<sup>14</sup>

Before randomization, between August 1982 and December 1984, potential participants were asked to provide base-line blood samples during a 16-week run-in period during which all subjects were given aspirin and none received placebo. Blood-collection kits, including EDTA Vacutainer tubes, were sent to participants with instructions for taking blood. Participants were asked to have their blood drawn into the EDTA tubes, centrifuge the tubes, and return the plasma (accompanied by a cold pack provided to participants) by overnight courier. The specimens were then divided into aliquots and stored at  $-80^{\circ}\text{C}$ . Of the 22,071 participants in the Physicians' Health Study, 14,916 (68 percent) provided base-line plasma samples. Over the 14 years of the trial, no specimen inadvertently thawed during storage.

### Confirmation of End Points and Selection of Controls

We requested hospital records (and for fatal events, death certificates and autopsy reports) for all reported cases of myocardial infarction, stroke, and venous thrombosis. The records were reviewed by a committee of physicians using standardized criteria to confirm or refute reported events. Reviewers of end points were unaware of treatment assignments.

Reported myocardial infarction was confirmed if its symptoms met World Health Organization (WHO) criteria and it was associated with either elevated plasma concentrations of enzymes or characteristic electrocardiographic changes. Silent myocardial infarctions were not included, since they could not be dated accurately. Deaths due to coronary disease were confirmed on the basis of autopsy reports, symptoms, circumstances of death, and a his-

tory of coronary disease. Reported stroke was confirmed on the basis of medical records showing a neurologic deficit of sudden or rapid onset that persisted for more than 24 hours or until death. Strokes were classified as ischemic or hemorrhagic. Computed tomographic scans were available for more than 95 percent of the confirmed strokes. Reported deep venous thrombosis was confirmed by the documentation of a positive venography study or a positive ultrasound study; deep venous thromboses documented only by impedance plethysmography or Doppler examination without ultrasound were not considered confirmed. Reported pulmonary embolism was confirmed by a positive angiogram or a completed ventilation-perfusion scan demonstrating at least two segmental perfusion defects with normal ventilation.

Each participant who provided an adequate base-line plasma sample and had a confirmed myocardial infarction, stroke, or venous thrombosis after randomization was matched with one control. Controls were participating physicians who provided base-line plasma samples and reported no cardiovascular disease at the time the patient reported his event. Controls were selected randomly from among study participants who met the matching criteria of age ( $\pm 1$  year), smoking status (smoking currently, smoked in the past, or never smoked), and length of time since randomization (in 6-month intervals). Using these methods, we evaluated 543 patients and 543 controls in this prospective, nested, case-control study.

### Laboratory Analysis

For each patient and control, plasma collected and stored at base line was thawed and assayed for C-reactive protein by enzyme-linked immunosorbent assay (ELISA) based on purified protein and polyclonal anti-C-reactive protein antibodies (Calbiochem).<sup>15</sup> Antibodies were used to coat microtiter-plate wells, and biotinylated C-reactive protein, together with the patient's plasma, was diluted 1:700 in assay buffer (phosphate-buffered saline with 0.1 percent Tween 20 and 1 percent bovine serum albumin). The excess was then washed off and the amount of biotinylated protein estimated by the addition of avidin-peroxidase (Vectastain, Vector Laboratories). Purified C-reactive protein was used as the standard, with protein concentrations as determined by the manufacturer. The C-reactive protein assay was standardized according to the WHO First International Reference Standard and had a sensitivity of 0.08  $\mu\text{g}$  per microliter, with a standard reference range of between 0.5 and 2.5 mg per liter. Methods used to measure plasma total and high-density lipoprotein (HDL) cholesterol, triglyceride, lipoprotein(a), total homocysteine, fibrinogen, D-dimer, and endogenous tissue plasminogen activator (t-PA) antigen have been described elsewhere.<sup>16-18</sup>

Blood specimens were analyzed in blinded pairs, with the position of the patient's specimen varied at random within the pairs to reduce the possibility of systematic bias and decrease interassay variability. The mean coefficient of variation for C-reactive protein across assay runs was 4.2 percent.

### Statistical Analysis

Means or proportions for base-line risk factors were calculated for patients and controls. The significance of any difference in means was tested by using Student's *t*-test, and the significance of any differences in proportions was tested by using the chi-square statistic. Because C-reactive protein values are skewed, median concentrations were computed and the significance of any differences in median values between patients and controls was assessed by using Wilcoxon's rank-sum test. Geometric mean concentrations of C-reactive protein were also computed after log transformation that resulted in nearly normal distribution. We used tests for trend to assess any relation of increasing C-reactive protein values with the risk of future vascular disease after dividing the sample into quartiles defined by the distribution of the control values. We obtained adjusted estimates by using conditional logistic-regression models that accounted for the matching variables and controlled for the random treatment assignment.

body-mass index, diabetes, history of hypertension, and parental history of coronary artery disease. Similar models were employed to adjust for measured base-line plasma concentrations of total and HDL cholesterol, triglyceride, lipoprotein(a), t-PA antigen, fibrinogen, D-dimer, and homocysteine. To evaluate whether aspirin affected these relations, analyses were repeated for all cases of myocardial infarction occurring on or before January 25, 1988—the date when randomized aspirin assignment was terminated. All *P* values are two-tailed, and confidence intervals were calculated at the 95 percent level.

### RESULTS

Table 1 shows the base-line characteristics of the study participants. As expected, those in whom myocardial infarction subsequently developed were more likely than those who remained free of vascular disease to have a history of hypertension or hyperlipidemia or a parental history of coronary artery disease. Similarly, those in whom stroke subsequently developed were more likely to be hypertensive. Because of the matching, patients and controls were similar in age and history of smoking.

Geometric mean and median plasma concentrations of C-reactive protein at base line were significantly higher among those in whom any vascular event subsequently developed than among those who remained free of vascular disease ( $P < 0.001$ ). The difference between patients and controls was greatest for those in whom myocardial infarction subsequently developed (1.51 vs. 1.13 mg per liter,  $P = 0.001$ ), although differences were also significant for stroke ( $P = 0.03$ ), particularly ischemic stroke ( $P = 0.02$ ). In contrast, concentrations of C-reactive protein were not significantly higher among those in whom venous thrombosis subsequently developed ( $P = 0.34$ ) (Table 2).

The relative risk of first myocardial infarction increased significantly with each increasing quartile of

base-line concentrations of C-reactive protein (*P* for trend across quartiles,  $< 0.001$ ), in such a way that the men in the highest quartile had a risk of future myocardial infarction almost three times that among those in the lowest quartile (relative risk, 2.9; 95 percent confidence interval, 1.8 to 4.6;  $P < 0.001$ ) (Table 3). Similarly, men with the highest base-line C-reactive protein values had twice the risk of future ischemic stroke (relative risk, 1.9; 95 percent confidence interval, 1.1 to 3.3;  $P = 0.02$ ). No significant associations were observed for venous thrombosis. The findings were similar in analyses limited to non-fatal events.

To evaluate whether increased base-line C-reactive protein values were associated with early rather than late thrombosis, we stratified the analysis of myocardial infarction according to the number of years of follow-up. The relative risk of future myocardial infarction that was associated with the highest quartile of C-reactive protein (as compared with the lowest quartile) ranged from 2.4 for events occurring in the first two years of follow-up to 3.2 for events occurring six or more years into follow-up (Table 4). Similarly, the relative risk of future myocardial infarction that was associated with a one-quartile change in the C-reactive protein concentration was stable over long periods (Fig. 1).

Smokers had significantly higher median concentrations of C-reactive protein than nonsmokers (2.20 vs. 1.19 mg per liter,  $P < 0.001$ ). By matching patients and controls for smoking status, we minimized the potential for confounding by smoking. To assess for effect modification, however, we repeated the analyses, limiting the cohort to nonsmokers. As Table 3 also shows, the relative risk of future myocardial infarction among nonsmokers increased sig-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PARTICIPANTS.

CHARACTERISTICS	CARDIOVASCULAR DISEASE DURING FOLLOW-UP*				
	NONE (N=543)	ANY (N=543)	MYOCARDIAL INFARCTION (N=246)	STROKE (N=196)	VENOUS THROMBOSIS (N=101)
Age (yr)	59±9.1	59±9.2	58±8.6	62±9.1	57±9.4
Smoking status (%)					
Never smoked	44	44	45	42	50
Smoked in the past	41	41	40	40	44
Currently a smoker	15	15	15	18	6
Diabetes (%)	4	7	5	12	2
Body-mass index†	25±2.6	26±3.2	26±3.3	25±3.2	26±2.9
History of high plasma cholesterol (%)	9	13	17	10	7
History of hypertension (%)	16	29	27	35	20
Parental history of coronary artery disease (%)	10	13	17	11	8

\*Plus-minus values are means ±SD.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

TABLE 2. BASE-LINE PLASMA CONCENTRATIONS OF C-REACTIVE PROTEIN IN STUDY PARTICIPANTS WHO REMAINED FREE OF VASCULAR DISEASE DURING FOLLOW-UP (CONTROLS) AND IN THOSE IN WHOM MYOCARDIAL INFARCTION, STROKE, OR VENOUS THROMBOSIS DEVELOPED (PATIENTS).

CARDIOVASCULAR DISEASE DURING FOLLOW-UP	PLASMA C-REACTIVE PROTEIN			
	GEOMETRIC MEAN	P VALUE	MEDIAN	P VALUE
	mg/liter		mg/liter	
None (n=543)	1.10	—	1.13	—
Any vascular event (n=543)	1.37	<0.001	1.40	<0.001
Myocardial infarction (n=246)	1.48	<0.001	1.51	<0.001
Any stroke (n=196)	1.30	0.03	1.36	0.03
Ischemic stroke (n=154)	1.36	0.01	1.38	0.02
Venous thrombosis (n=101)	1.24	0.22	1.26	0.34

TABLE 3. RELATIVE RISK OF FUTURE MYOCARDIAL INFARCTION, STROKE, AND VENOUS THROMBOSIS ACCORDING TO BASE-LINE PLASMA CONCENTRATIONS OF C-REACTIVE PROTEIN.

VASCULAR EVENT*		QUANTILE OF C-REACTIVE PROTEIN CONCENTRATION (mg/liter)				P FOR TREND
		<0.55	0.55-1.14	1.15-2.10	>2.11	
Myocardial infarction (total cohort)	Relative risk	1.0	1.3	2.6	2.9	<0.001
	95% CI	—	1.1-2.9	1.6-4.3	1.8-4.6	
	P value	—	—	<0.001	<0.001	
Myocardial infarction (nonsmokers)	Relative risk	1.0	1.7	2.6	2.8	<0.001
	95% CI	—	1.0-2.8	1.5-4.1	1.7-4.7	
	P value	—	—	<0.001	<0.001	
Ischemic stroke (total cohort)	Relative risk	1.0	1.2	1.9	1.9	0.03
	95% CI	—	0.8-2.8	1.1-3.2	1.1-3.3	
	P value	—	0.07	0.02	0.02	
Venous thrombosis (total cohort)	Relative risk	1.0	1.1	1.2	1.3	0.28
	95% CI	—	0.6-3.0	0.7-2.3	0.7-2.4	
	P value	—	0.78	0.51	0.42	

\*CI denotes confidence interval.

TABLE 4. RELATIVE RISK OF FIRST MYOCARDIAL INFARCTION ASSOCIATED WITH THE HIGHEST QUARTILE OF BASE-LINE PLASMA C-REACTIVE PROTEIN CONCENTRATIONS AS COMPARED WITH THE LOWEST QUARTILE, ACCORDING TO THE YEAR OF STUDY FOLLOW-UP.

GROUP*	FOLLOW-UP (YR)			
	0-2	3-4	4-6	>6
Total cohort				
Relative risk	2.4	2.9	2.8	3.2
95% CI	0.9-6.8	1.1-7.6	1.1-6.9	1.3-8.5
P value	0.09	0.03	0.03	0.02
Nonsmokers				
Relative risk	2.8	2.9	2.7	2.9
95% CI	0.9-8.7	1.0-8.3	1.0-7.0	1.1-8.3
P value	0.07	0.05	0.05	0.04

\*CI denotes confidence interval.

nificantly with each increasing quartile of C-reactive protein (P for trend, <0.001). Similarly, the long-term effects of the concentration of C-reactive protein on the risk of myocardial infarction were virtually identical among nonsmokers (Table 4). Moreover, the relation between the concentration of C-reactive protein and myocardial infarction was not significantly altered in analyses that adjusted for body-mass index; the presence or absence of diabetes, hypertension, or a family history of premature coronary artery disease; and the plasma concentrations of total cholesterol, HDL cholesterol, triglycerides, lipoprotein(a), t-PA antigen, D-dimer, fibrinogen, or homocysteine (Table 5).

Finally, to assess whether the beneficial effect of aspirin on the risk of myocardial infarction varied according to the base-line level of C-reactive protein, we repeated these analyses for events occurring before January 25, 1988, the date when randomized aspirin treatment was terminated.

The risk of future myocardial infarction increased with each increasing quartile of C-reactive protein values for men randomly assigned to either aspirin or placebo, and the rates of myocardial infarction were lower in the aspirin group for all quartiles of C-reactive protein (Fig. 2). However, the magnitude of the beneficial effect of aspirin in preventing myocardial infarction was directly related to base-line levels of C-reactive protein. Specifically, randomized aspirin assignment was associated with a large and statistically significant reduction in the risk of myocardial infarction among men with base-line levels of C-reactive protein in the highest quartile (risk reduction, 55.7 percent; P=0.02). Among those with base-line levels of C-reactive protein in the lowest quartile, however, the reduction in risk associated with aspirin was far smaller and no longer statistically significant (risk reduction, 13.9 percent; P=0.77). These effects were linear across quartiles, so that the apparent benefit of aspirin diminished in magnitude with each decreasing quartile of inflammatory risk (Fig. 2). This finding remained essentially unchanged after further adjustment for other coronary risk factors, and the interaction between assignment to the aspirin group and base-line levels of C-reactive protein (treated as a log-transformed continuous variable) was statistically significant (P=0.048).

## DISCUSSION

These prospective data indicate that the base-line plasma concentration of C-reactive protein in apparently healthy men can predict the risk of first myocardial infarction and ischemic stroke. In addition, the risk of arterial thrombosis associated with the level of C-reactive protein was stable over long periods and was not modified by other factors, including smoking status, body-mass index, blood pressure, or the plasma concentration of total or HDL cholesterol, tri-

glyceride, lipoprotein(a), t-PA antigen, D-dimer, fibrinogen, or homocysteine. In contrast, the benefits of aspirin in reducing the risk of a first myocardial infarction diminished significantly with decreasing concentrations of C-reactive protein — an intriguing finding, since this substance has antiinflammatory as well as antiplatelet properties. Finally, there was no significant association for venous thromboembolism, suggesting that the relation of inflammation to vascular risk may be limited to the arterial circulation.

Because blood samples were collected at base line, we can exclude the possibility that acute ischemia affected levels of C-reactive protein. Furthermore, the statistically significant associations observed were present among nonsmokers, indicating that the effect of C-reactive protein on vascular risk is not simply the result of cigarette smoking.<sup>11,12</sup> Thus, our prospective data relating base-line levels of C-reactive protein to future risks of myocardial infarction and stroke among apparently healthy men greatly

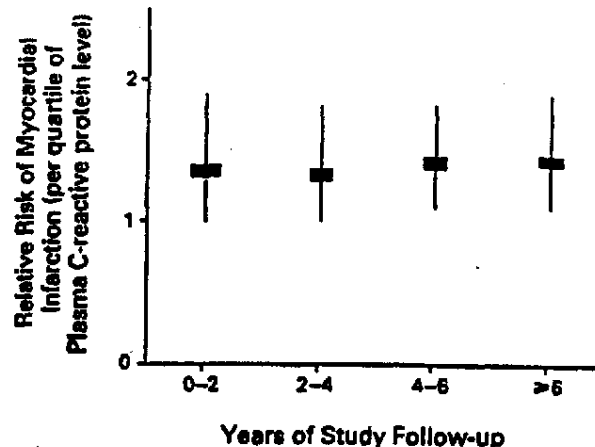


Figure 1. Relative Risk (and 95 Percent Confidence Intervals) of a First Myocardial Infarction Associated with Each Increasing Quartile of Base-Line C-Reactive Protein Values, According to the Year of Study Follow-up.

TABLE 1. RELATIVE RISK OF FUTURE MYOCARDIAL INFARCTION, ACCORDING TO BASE-LINE PLASMA CONCENTRATIONS OF C-REACTIVE PROTEIN, ADJUSTED FOR LIPID AND NONLIPID VARIABLES.\*

VARIABLES ADJUSTED FOR	QUANTILE OF C-REACTIVE PROTEIN CONCENTRATION (mg/liter)				P FOR TREND
	<0.55	0.56-1.14	1.15-2.10	≥2.11	
Total HDL cholesterol					
Adjusted relative risk	1.0	1.8	2.2	2.3	0.002
95% CI	—	1.0-3.1	1.3-3.7	1.4-3.9	
P value	—	0.05	0.004	0.002	
Triglycerides					
Adjusted relative risk	1.0	1.8	2.1	2.3	<0.001
95% CI	—	1.0-3.2	1.3-3.7	1.6-4.9	
P value	—	0.06	0.008	<0.001	
Lipoprotein(a)					
Adjusted relative risk	1.0	2.0	2.3	2.5	<0.001
95% CI	—	1.2-3.4	1.5-4.2	1.5-4.2	
P value	—	0.01	<0.001	<0.001	
t-PA antigen					
Adjusted relative risk	1.0	1.7	1.9	2.9	0.002
95% CI	—	0.9-3.4	1.0-3.6	1.5-5.6	
P value	—	0.13	0.06	0.002	
Total homocysteine					
Adjusted relative risk	1.0	1.8	2.9	3.6	<0.001
95% CI	—	1.1-3.1	1.7-4.6	2.1-5.9	
P value	—	0.02	<0.001	<0.001	
D-Dimer					
Adjusted relative risk	1.0	2.2	2.4	2.7	0.001
95% CI	—	1.2-4.1	1.3-4.2	1.5-4.7	
P value	—	0.007	0.003	<0.001	
Fibrinogen					
Adjusted relative risk	1.0	2.2	2.2	2.9	0.01
95% CI	—	1.1-4.7	1.0-4.4	1.4-5.9	
P value	—	0.04	0.04	0.005	
Body-mass index, diabetes, history of hypertension, and family history of coronary artery disease					
Adjusted relative risk	1.0	1.5	2.4	2.6	<0.001
95% CI	—	0.9-2.5	1.5-4.0	1.6-4.4	
P value	—	0.14	<0.001	<0.001	

\*All models were further adjusted for random assignment of patients to receive aspirin and beta carotene. CI denotes confidence interval.

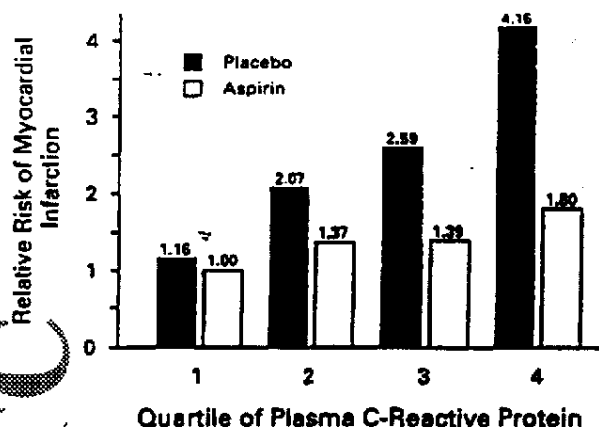


Figure 2. Relative Risk of a First Myocardial Infarction Associated with Base-Line Plasma Concentrations of C-Reactive Protein Stratified According to Randomized Assignment to Aspirin or Placebo Therapy.

Analyses are limited to events occurring before the unblinding of the aspirin component of the Physicians' Health Study. The reduction in the risk of myocardial infarction associated with the use of aspirin was 13.9 percent in the first (lowest) quartile of C-reactive protein values, 25.9 percent in the second quartile, 45.3 percent in the third quartile, and 55.7 percent in the fourth (highest) quartile.

extend previous observations from studies of acutely ill patients,<sup>9</sup> patients with symptomatic coronary disease,<sup>10</sup> or those at high risk partly because of cigarette smoking.<sup>11</sup> Moreover, in these data, the effects of C-reactive protein were independent of a large number of lipid-related and non-lipid-related risk factors.

The mechanism that relates the level of C-reactive protein to atherothrombosis is unclear. Previous infection with *Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex virus, or cytomegalovirus may be a source of the chronic inflammation detected by C-reactive protein.<sup>21-27</sup> It is also possible that C-reactive protein is a surrogate for interleukin-6,<sup>28</sup> a cellular cytokine associated with the recruitment of macrophages and monocytes into atherosclerotic plaques.<sup>29</sup> In addition, C-reactive protein can induce monocytes to express tissue factor, a membrane glycoprotein important in initiating coagulation.<sup>30</sup> Finally, it had been hypothesized that bronchial inflammation due to smoking was responsible for associations seen in previous studies relating C-reactive protein to vascular risk.<sup>11</sup> In this regard, our observation that the effect of C-reactive protein is present among nonsmokers makes bronchial inflammation a less likely mechanism. Furthermore, the finding that the effects are stable over long periods suggests that short-term effects on clotting are unlikely.

Our data regarding the interrelation of C-reactive protein and aspirin merit careful consideration. In

the Physicians' Health Study, aspirin reduced the risk of a first myocardial infarction by 44 percent.<sup>12</sup> The present findings indicate that the effect of aspirin in preventing a first myocardial infarction was greatest among the men with the highest base-line C-reactive protein concentrations and that the benefit diminished significantly with decreasing concentrations of this inflammatory marker. Thus, although the antiplatelet effects of aspirin may be modified by underlying inflammation, these data also suggest the possibility that the benefit of aspirin may have been due, at least in part, to antiinflammatory effects.<sup>31</sup> Alternatively, patients with large inflammatory burdens may have a distinct vascular mechanism leading to thrombosis that is affected differently by aspirin therapy. For example, the protective effect of aspirin may differ in the setting of plaque rupture as compared with focal endothelial erosion.<sup>32,33</sup>

The potential limitations of these data also merit consideration. First, our analyses are based on a single base-line determination that may not accurately reflect inflammatory status over long periods. Furthermore, although coefficients of variation were low, misclassification due to laboratory error cannot be ruled out. It is important to note, however, that neither of these sources of variability can account for the observed associations, since any random misclassification would bias results toward the null hypothesis. Since our study was limited to measures of C-reactive protein, other prospective studies evaluating specific cytokines, cellular adhesion molecules, and chronic infectious agents will be required to further elucidate the role of inflammation in the initiation and progression of atherosclerosis.

We draw four main conclusions from these data. First, among apparently healthy men, the base-line level of inflammation as assessed by the plasma concentration of C-reactive protein predicts the risk of a first myocardial infarction and ischemic stroke, independently of other risk factors. Second, the base-line concentration of C-reactive protein is not associated with the risk of venous thrombosis, a vascular event generally not associated with atherosclerosis. Third, C-reactive protein is not simply a short-term marker of risk, as has previously been demonstrated in patients with unstable angina,<sup>9</sup> but is also a long-term marker of risk, even for events occurring six or more years later. This observation suggests that the effects of inflammation are probably mediated through a chronic process and excludes the possibility that undetected acute illness at base line is responsible for the observed effects. Finally, the benefits of aspirin appear to be modified by underlying inflammation — an observation that raises the possibility of antiinflammatory as well as antiplatelet effects of this agent. The latter observation also suggests the possibility that other antiinflammatory agents may have a role in preventing cardiovascular

disease. Moreover, these data suggest that inflammatory markers such as C-reactive protein may provide a method of identifying people for whom aspirin is likely to be more or less effective — a hypothesis requiring direct testing in randomized trials.

Supported by grants (HL-26490, HL-34595, HL-46696, CA-34944, CA-42182, and CA-40360) from the National Institutes of Health. Dr Ridker is supported by a Clinician Scientist Award from the American Heart Association.

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## Changing Mortality from Coronary Heart Disease among Smokers and Nonsmokers over a 20-Year Interval<sup>1</sup>

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A comparison of coronary heart disease (CHD) mortality in two large American Cancer Society studies, Cancer Prevention Study (CPS) I (1959-1965) and CPS-II (1982-1988) suggests that surprisingly large declines occurred in both groups so defined to minimize the influence of change of smoking status. CHD mortality fell essentially in half when comparing nearly 300,000 persons who were actively smoking cigarettes at entry into CPS-I with about 228,000 persons who were similarly actively smoking at entry into CPS-II, about 20 years later. CHD mortality also declined by more than 50% among nearly half a million lifelong nonsmokers recruited for CPS-I in the early 1960s and for CPS-II in the mid-1980s. Possible explanations for these large declines include unmeasured decreases in smoking related to trial design, errors in ascertainment of causes of death, greater improvement among smokers of their risk factors for CHD, and changes in cigarettes or the pattern of smoking that have been salutary for CHD, but not for lung disease or lung cancer; none of these putative explanations can be supported by data from these studies. CHD mortality, much lower in absolute terms in recent years, is still much higher among smokers vs nonsmokers, so that the beneficial trends observed from CPS-I to CPS-II should stimulate further exploration of how CHD is related to smoking, and not serve as an excuse to ignore continued smoking. © 1997 Academic Press

**Key Words:** smoking; coronary heart disease.

### INTRODUCTION

A recent report comparing mortality rates in two large American Cancer Society (ACS) studies, Cancer Prevention Studies I and II (CPS-I and CPS-II) provided the opportunity to examine changes in death rates from coronary heart disease (CHD) between the early 1960s and the mid-1980s [1]. From CPS-I, covering the period from 1959 to 1965, to CPS-II, 1982 to 1988, age-adjusted death rates from CHD declined by

approximately 50% among men and women, among smokers as well as nonsmokers. Table 1 documents the magnitude of the decline in the two groups analyzed, lifelong nonsmokers vs those who were smoking cigarettes at the time of enrollment into each study. In both groups, CHD mortality fell essentially by half in the 20+ years between CPS-I and CPS-II. Although it has been well recognized that incidence and mortality rates for CHD have been declining for many years, the analysis of Thun et al. [1], contrasting results for continuing smokers with those of lifelong nonsmokers, and excluding those who quit smoking, suggests that major recent declines in CHD may be independent of changes in smoking patterns. This paper attempts to explain this surprising conclusion.

Although cited elsewhere in this compilation of papers [2], basic characteristics of CPS-I and CPS-II should be noted. These two trials were done by ACS volunteers who recruited friends, neighbors, acquaintances, and their households to fill out questionnaires at entry. Questionnaires were distributed within a brief time window to adults over age 30 if at least one person in the household was over age 45. Follow-up for ascertaining deaths then occurred over subsequent years, and causes of death were obtained from death certificates. The composition of the volunteer research force as well as the entry criteria resulted in a population that was by no means representative, but rather was >90% white, mainly middle class, older, more educated, more often married, and less urban than the general U.S. population. There was also some excess of people with past cancer. CPS-I was done in 25 states, CPS-II in all 50 states; in both instances more than 1 million questionnaires formed the initial research cohort. The questionnaires included medical, demographic, and lifestyle characteristics, including current smoking pattern. Current smokers were asked the number of cigarettes smoked daily at the time of enrollment; past consumption was not considered. Changes in smoking habits (or for that matter, changes in any other characteristics) during the follow-up period were not assessed. There was neither medical examination nor laboratory testing, so there

<sup>1</sup> Presented at the American Health Foundation AHF/NCI/ACS Workshop, New York, New York, April 15, 1996.

TABLE 1  
Changes in CHD Death Rates between CPS-I and CPS-II (per 100,000 person years)

	Men			Women		
	CPS-I 1959-1965	CPS-II 1982-1988	%Δ	CPS-I 1959-1965	CPS-II 1982-1988	%Δ
Lifelong nonsmokers	681	294	-57%	306	118	-61%
Smokers at enrollment	1,168	548	-53%	419	215	-49%

Note. Adapted from Thun et al. [1].

are no data on measured blood pressure, serum cholesterol, high-density lipoprotein or other lipids, obesity, exercise tolerance, or diabetes. Finally, the main analysis of Thun et al. [1] excluded former smokers, those who had ever smoked pipes or cigars, and those whose daily cigarette consumption or duration could not be determined, leaving just current smokers vs lifelong nonsmokers; these exclusions totalled about 25% of the original CPS-I cohort and about 40% of the original CPS-II cohort.

Several expert conferences have been held at the National Heart, Lung, and Blood Institute [3-5] to attempt to explain the striking decline in CHD incidence and mortality that has occurred in the United States and elsewhere since approximately 1950. There is a general consensus that the cause for the decline is multifactorial, and attempts have been made to identify the most important causes. In one such attempt, by Goldman and Cook, attributed 24% of the decline in CHD mortality from 1968 to 1976 to reduction in smoking [6]. This, then, is the potential paradox: if many authorities attribute a considerable portion of the decline in CHD to a reduction in smoking, how is one to explain major and proportionate declines in CHD mortality from CPS-I in the early 1960s to CPS-II in the mid-1980s in two populations defined to minimize any change in smoking status: the first group comprising those who were actively smoking cigarettes at the time of entry into either CPS-I or CPS-II, and the second group defined as lifelong nonsmokers and thus not smoking at entry into either study? Why did CHD mortality decline so much in those who continued to smoke, without any cessation of smoking, to explain part of the decline? And, why did CHD mortality decline so substantially in the lifelong nonsmokers, since there can be no contribution from giving up smoking in those who never smoked to begin with?

There is no dearth of possible etiologic causes for major declines in CHD incidence or mortality from the early 1960s to the mid-1980s; the most important possibilities are summarized here with comments about relationships to smoking status and particularly how the various factors might explain a decline in smokers' CHD mortality that was proportionately similar to that of nonsmokers.

#### IMPROVED THERAPY OF ACUTE MYOCARDIAL INFARCTION (MI)

There seems little doubt that the case fatality rate for acute MI has fallen substantially during the time frame between CPS-I and CPS-II [7], which is presumably due to the increasing and now nearly universal availability of CCUs, as well as major increases in the proportion of patients treated with thrombolytic therapy, coronary angiography, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass surgery (CABG). Other medical therapies of myocardial infarction (e.g., recognition of the major role of acute aspirin [8], acute use of beta blockers [9], possibly increased use of intravenous heparin and nitroglycerin) may also play a role. There are suggestions of differential effects of some therapies among smokers, and nonsmokers, particularly thrombolytic agents and aspirin. For example, the Thrombolysis in Myocardial Infarction II study analyzed multiple baseline variables in 3,339 patients with acute MI treated with TPA and found smokers to have significantly lower early mortality [10,11] as well as reinfarction rates for up to 3 years after the initial MI [12] compared with nonsmokers. Although the lower early mortality among smokers was explained by a lesser burden of other risk factors (cigarette smoking increases platelet function and thrombogenicity so smokers are thought to develop acute MI at an earlier age with fewer other risk factors and thus are presumed better able to tolerate the insult [10]), the significantly lower reinfarction rate among smokers persisted even after multivariate adjustment for other risk factors [10,12]. The somewhat counterintuitive observation remains unexplained, but it is conceivable that smokers do indeed fare proportionately better than their nonsmoking counterparts for some acute CHD conditions in the modern era especially after thrombolytic therapy or aspirin, thus providing a partial explanation why more recent CHD death rates have declined as much among smokers as among nonsmokers.

#### IMPROVED THERAPY OF UNSTABLE ANGINA

Although it is difficult to prove statistically that there has been a decrease in morbidity or mortality

from this condition whose definition is much less exact than acute MI, there have certainly been major changes in the therapy of unstable angina. The most likely to have produced improvements during the 20-year period discussed herein are the increased use of intravenous heparin [13,14], aspirin [15], and possibly cardiac catheterization and invasive therapy (see chronic stable angina, below).

#### IMPROVED EMERGENCY CARE

The increased availability and training of emergency prehospital services, an increased emphasis on education of the public to the early warning signs of acute MI, and the increased teaching of cardiopulmonary resuscitation to the public and to health providers may all play some role. There is no reason to presume any differential effect among smokers vs nonsmokers.

#### IMPROVED MEDICAL AND SURGICAL THERAPY OF CHRONIC ISCHEMIC HEART DISEASE

The standard of care for stable angina or the post-MI patient has changed greatly from the early 1960s to the mid-1980s, with enormous increases in the utilization of cardiac catheterization, PTCA, and CABG [16]. Although it is difficult to quantify the statistical improvement from various therapies, there are certainly subgroups in which the newer therapies are likely to have improved survival, e.g., patients with left main or triple vessel coronary artery disease with left ventricular dysfunction. Given the likely adverse effects on mortality of type 1 anti-arrhythmic drugs, declining use of these drugs (e.g., quinidine and flecainide) might also have contributed to a fall in CHD mortality [although the general physician population first became aware of the dangers of these drugs with publication of the Cardiac Arrhythmia Suppression Trial in 1989 [17], so that it is unlikely that less anti-arrhythmic drug use had much effect between the 1960s and the mid-1980s]. Calcium blockers, widely used in the United States for hypertension as well as angina after the introduction of verapamil in the late 1970s, are probably neutral for most patients with CHD, but possibly not beneficial for some subgroups, so it seems unlikely that their use would have had much beneficial effect on CHD mortality; a possible adverse effect is the subject of much current controversy [18]. One other change in drug therapy that may have helped to decrease CHD mortality is the increasing use of angiotensin-converting enzyme (ACE) inhibitors. Captopril was introduced in 1981 for hypertension, and various ACE inhibitors were used throughout the 1980s for that condition. However, it is now clear that ACE inhibitors improve survival among patients with overt congestive heart failure (CHF) [19], poor ventricular function without overt CHF [20], and post-MI [21]—so that their increasing use, even if for hypertension,

likely had a beneficial effect in reducing morbidity and mortality due to CHD since the early 1980s. There is nothing to suggest a differential effect favoring smokers (in order to help explain the "paradox" cited above) of any of these therapies.

#### IMPROVEMENTS IN CORONARY RISK FACTORS

In the past 20–30 years and during the interval between CPS-I and CPS-II there has been considerable increase in the number of patients who are aware of their hypertension and whose blood pressure is controlled by drug therapy [22]. The prevalence of hyperlipidemia (defined by the National Cholesterol Education Program [23]) fell considerably during the period discussed herein [24], and the average serum cholesterol fell by about 7 mg/dl (white men) and 9 mg/dl (white women) in one study [25]. There were also changes in the U.S. diet in the general direction of the "prudent diet," with considerable declines in eggs, meat, and animal fat and oil consumption and considerable increases in fish, poultry and vegetable fat and oil consumption [26]. On the other hand, not all CHD risk factors showed favorable trends; the prevalence of obesity changed very little or actually worsened [24]. It is not clear that the U.S. population as a whole has substantially changed its level of physical exercise, although it is possible that the better educated group of the CPS-I and CPS-II might have done so. There has been interest in the use of antioxidants, and some suggestive data that vitamin E may be beneficial in the primary prevention of CHD [27,28], but it is unclear how widespread was the practice of taking antioxidants before the mid-1980s. Perhaps more important is the increase in the use of low-dose aspirin as a prophylactic measure for the primary prevention of CHD, although much of that increase probably occurred only after 1989 with publication of the Physician's Health Study documenting benefits of low-dose aspirin [29]. Finally, there was far more use of hormone replacement therapy (HRT) among postmenopausal women in the later time period, but since smokers are less likely to use HRT [30,31] this factor would not explain comparable declines in CHD among continuing smokers vs nonsmokers.

It is important to note that risk factor reduction is likely related to socioeconomic and educational status, so that the more middle class, nonminority, and probably more health-conscious participants in CPS-I and CPS-II are likely to have achieved substantially more risk factor reduction than the U.S. population as a whole, and thus might have enjoyed greater beneficial effect on CHD mortality from risk factor reduction. There are no data suggesting that risk factor reduction has been more vigorous in smokers vs nonsmokers, except that obesity, which has increased in the general population in recent years, probably is less common in

smokers (one recent study showed an extra 4.4- to 5-kg weight gain over a 10-year period in quitters vs continuing smokers [32]). Since by the 1980s there was probably more public knowledge that the effect of multiple CHD risk factors was much greater than that of a single risk factor, it is barely conceivable that those who chose to continue smoking might have decided to reduce other risk factors more than those virtuous souls who, never having smoked, were less focused on other CHD risk factors. On the other hand, since many more former smokers were excluded from CPS-II (22% of the total vs 7% excluded for that reason in CPS-I), those remaining smokers by the 1980s were more likely "hard core," and this resistance to a healthy lifestyle might have spilled over into other "coronary-prone behavior." Continuing smokers are known to be notoriously non-health conscious in many ways. Although data from CPS-I and CPS-II, obtained solely at entry, cannot determine the status of other risk factors during the course of each study, it seems highly unlikely that smokers would have differentially reduced other coronary risk factors in later years in comparison with nonsmokers.

#### CHANGES IN SMOKING HABITS

Perhaps, there was a change in smoking, especially in the later study, that was missed by the methodology of the studies. This would likely have been due to a greater decrease in cigarette consumption or actual quitting in the smokers of CPS-II after study enrollment. The classification of "smoker," done at enrollment alone in both studies, was more inaccurate as CPS-II progressed than it was during CPS-I. This seems quite plausible as there were much greater societal pressures to cut down or quit smoking in the 1980s compared with the 1960s. This is additionally attractive as an explanation since we now know that declines in CHD incidence or mortality can be seen within a year or two after quitting smoking [33,34], possibly because smoking has acute or subacute effects on thrombosis, coronary vasospasm, or other physiologic processes as opposed to effects on atherosclerosis or other processes that take longer to reverse. Possible changes in patterns of cigarette consumption are discussed below.

#### SECULAR TRENDS IN PASSIVE SMOKING

Secular trends in passive smoking may have accounted for some of the results. In particular, the greater reduction in CHD deaths among nonsmoking vs smoking women (61% decline from CPS-I to CPS-II among nonsmoking women, 49% decline from the 1960s to the 1980s among smoking women) might be due to more quitting and more restrictions on smoking among the public at large in the later time period, so that nonsmokers in the 1980s in CPS-II had less exposure to passive smoking than their 1960s counterparts.

Data to estimate passive smoke exposure are nonexistent in the CPS studies themselves, and even scarce for the United States as a whole in the earlier time period of CPS-I. In the Third National Health and Nutrition Examination Survey (NHNS III) [35], done from 1988 to 1991, slightly after CPS-II, 37% of adult non-tobacco users lived in a home with at least one smoker or reported environmental tobacco exposure at work. Blood levels in NHNS III showed an astonishing 87.9% of non-tobacco users to have detectable levels of cotinine, so the potential for an influence of passive smoking on nonsmokers is real. Passive smoking exposure almost certainly declined substantially from the 1960s to the 1980s: the National Health Interview Survey (NHIS) found 42% of the adult U.S. population to be smokers in 1965, vs 33.2% in 1980 and 28.1% in 1988 [36]. Thus secular reductions in passive smoking might help to explain CHD reductions among nonsmokers independent of their smoking status. It is harder to explain substantial or similar proportionate CHD reductions among continuing smokers on the basis of less passive smoking since passive smoking should be a much smaller proportion of smokers' overall exposure to tobacco.

#### ERRORS IN CHD MORTALITY RATES

The earlier CHD mortality rates may be less reliable because of inaccurate death certificate diagnoses. There was far more use of cardiac catheterization, nuclear stress tests, and other invasive and noninvasive modalities in making accurate diagnoses of CHD in the 1980s compared with the 1960s. Thus it is possible that there were more "wastebasket" diagnoses of CHD, especially among those known to be smokers, in the 1960s for CPS-I, whereas by the 1980s more accurate diagnoses led to fewer death certificates being signed out as CHD (especially among smokers, who could have been assumed to have CHD in uncertain circumstances, causing a spurious decline in CHD, more marked for smokers, between the two CPS studies).

There was also a change in the coding of cardiovascular diagnoses, with International Classification of Diseases (ICD)-7 in use during CPS-I and ICD-9 during CPS-II. Since the change in coding applied to both smokers and nonsmokers, it is hard to understand how the later ICD classification could have affected the ratio of CHD mortality or morbidity between the two groups. Conceivably, though, inclusion of more hypertensive diseases among deaths coded cardiovascular using ICD-9 in CPS-II could have altered the ratio of deaths if hypertension differentially causes less CHD mortality among smokers. This could have produced the statistical effect of causing CHD rates to decline more among smokers and producing a similar proportionate decline from CPS I (ICD-7) to CPS-II (ICD-9) among smokers and nonsmokers. There are no data to support any of these purely speculative hypotheses.

## CHANGES IN CIGARETTE COMPOSITION

Changes in cigarettes (including but not limited to the increasing use of filters) or in the pattern of cigarette smoking, which occurred between the 1960s and the 1980s, may have lowered the risk for CHD mortality among smokers but not for lung cancer and chronic obstructive pulmonary disease, since the mechanisms for cigarettes causing heart and lung disease might be quite different. Incomplete data do not particularly suggest major changes in smoking patterns. Although U.S. per capita cigarette consumption (by Department of Agriculture estimates from taxes paid and cigarettes imported) peaked at 4,345 cigarettes/year/U.S. adult  $\geq$  age 18 in 1963, the midpoint of CPS-I, fell steadily thereafter to 3,739 in 1982 and 3,096 in 1988 (the years of CPS-II), and reached a new low of 2,493 cigarettes/year in 1994 [36], these numbers reflect the falling number of smokers as well as the number of cigarettes per smoker. The NHIS uses interviews of a sample of the U.S. adult population, the earliest available data is from 1974 at which time the mean number of cigarettes self-reported by smokers was 19.8 per day, with no real change through 1988 (20.2) and perhaps a slight fall to 18.2 per day by the last survey in 1991 [36]. The percentage of smokers who were "heavy smokers" ( $\geq 25$  cigarettes/day) did not change from 1974 through 1988. Note that CHD and other death rates in Thun et al. [7] were standardized for cigarette consumption by comparing subjects who reported smoking exactly 20 or 40 cigarettes per day at the time of entry into CPS-I with their counterparts matched by sex and number of cigarettes smoked in CPS-II. Thus any secular trends in cigarette or tobacco consumption that could have affected outcomes differentially in the earlier vs the later time period would have had to occur after study entry (and thus been missed since there was no follow-up ascertainment after study entry of ongoing smoking patterns including daily consumption, quitting, brand changes, etc.).

## CONCLUSIONS

In summary, a comparison of CHD mortality rates from the early 1960s and the mid-1980s in two cohort questionnaire studies each involving more than 1,000,000 people suggests that surprisingly large declines occurred among those who continued to smoke, declines very similar to those observed among lifelong nonsmokers over the same time period. Many medical and social trends during that 20+ year time frame might be associated with reductions in CHD incidence or mortality, and the problem is to explain how continuing smokers might have achieved so large a proportionate decline despite continuing to smoke, a reduction essentially equal to that which was observed among lifelong nonsmokers. Possible explanations, among others, include unmeasured declines in smoking

related to the design of the trials, errors related to ascertainment of causes of death, and changes in cigarettes or the pattern of smoking that have been salutary for CHD even if not for lung disease or lung cancer. CHD mortality, even if much lower in absolute terms in recent years, continues to be much higher among smokers vs nonsmokers, so that the beneficial trends observed in these studies should stimulate the exploration of mechanisms of how CHD is related to smoking and not serve as an excuse for exposing smokers to relative risks of CHD that are still 1.5–2 times that of nonsmokers.

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## Review

## Chronic infections and coronary heart disease: is there a link?

John Danesh, Rory Collins, Richard Peto

A large number of studies have reported on associations of human coronary heart disease (CHD) and certain persistent bacterial and viral infections. We review the epidemiological and clinical evidence on CHD and *Helicobacter pylori*, *Chlamydia pneumoniae*, and cytomegalovirus (CMV), as well as possible mechanisms. The association between CHD and *H. pylori* may be accounted for by residual confounding from risk factors. Although the association between *C. pneumoniae* and CHD is stronger, the sequence of infection and disease is uncertain. As regards CMV, a limited number of patients with classic atherosclerotic coronary artery disease have been studied. Further studies are needed to resolve these uncertainties.

In the 1970s, experimental infection of germ-free chickens with an avian herpesvirus was found to produce arterial disease that resembled human atherosclerosis.<sup>1</sup> Associations have since been reported of human coronary heart disease (CHD) with certain gram-negative bacteria (eg, *Helicobacter pylori* and *Chlamydia pneumoniae*), with certain herpesviruses (particularly cytomegalovirus (CMV)), and with clinical markers of chronic dental infection (eg, severe periodontal disease and missing teeth<sup>2</sup>). Most of the published studies relate to *H. pylori*, *C. pneumoniae*, or CMV: some report evidence of bacteria or viruses in atheromatous and non-atheromatous blood vessels, but most are seroepidemiological studies based on antibody measurements. Our aim is to provide a systematic review of these epidemiological and clinical studies, along with a selected review of the experimental studies of possible mechanisms.

The proportion of adults in developed countries who have antibodies to *H. pylori*, *C. pneumoniae*, and CMV is about half (table). The presence of serum antibodies does not necessarily indicate the persistence of active infection at any site, or persistent exposure of the coronary arteries to any type of insult. High concentrations of IgG antibodies to *H. pylori* are, however, fairly reliable indicators of chronic gastric infection and, in the absence of specific treatment, they generally persist indefinitely from early life (when infection is usually acquired) and can be detected with greater than 90% accuracy. By contrast, *C. pneumoniae* antibody titres are less reliable indicators of persistent respiratory infection since they may fall substantially within a few years of seroconversion, and may increase substantially if reinfection occurs. Similarly, CMV antibody titres may fluctuate greatly owing to repeated reactivations of latent infection (table). Such temporal variation means that any associations between CHD and antibody titres

for *C. pneumoniae* and CMV measured at just one time will, owing to regression dilution,<sup>3</sup> be substantially weaker than associations of CHD with long-term average antibody concentrations, or with direct evidence of persistent infection at the relevant anatomical site.

Various potential causative mechanisms that may act either acutely (eg, precipitating plaque rupture) or chronically (eg, promoting plaque growth) have been proposed for the reported associations between infections and CHD (figure 1).<sup>4-12</sup> Some involve possible direct effects of infectious agents on the arterial wall, including endothelial injury<sup>4</sup> or dysfunction,<sup>5</sup> smooth-muscle proliferation,<sup>6</sup> and local inflammation.<sup>4</sup> But most involve possible indirect effects mediated in the circulation through chronic inflammation,<sup>7-10</sup> cross-reactive antibodies,<sup>4,11</sup> or changes in known or suspected cardiovascular risk factors (such as lipids,<sup>12,13</sup> coagulation proteins,<sup>9</sup> oxidative metabolites,<sup>9</sup> or homocysteine<sup>14</sup>).

## Review methods

Epidemiological and clinical studies published in any language before January, 1997, that reported on associations between

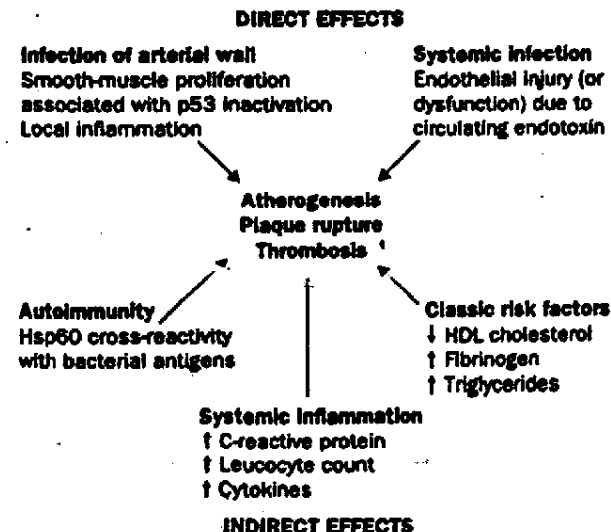


Figure 1: Postulated mechanisms to link infections and vascular disease

Hsp=heat-shock protein; HDL=high-density lipoprotein.

Lancet 1997; 350: 430-36

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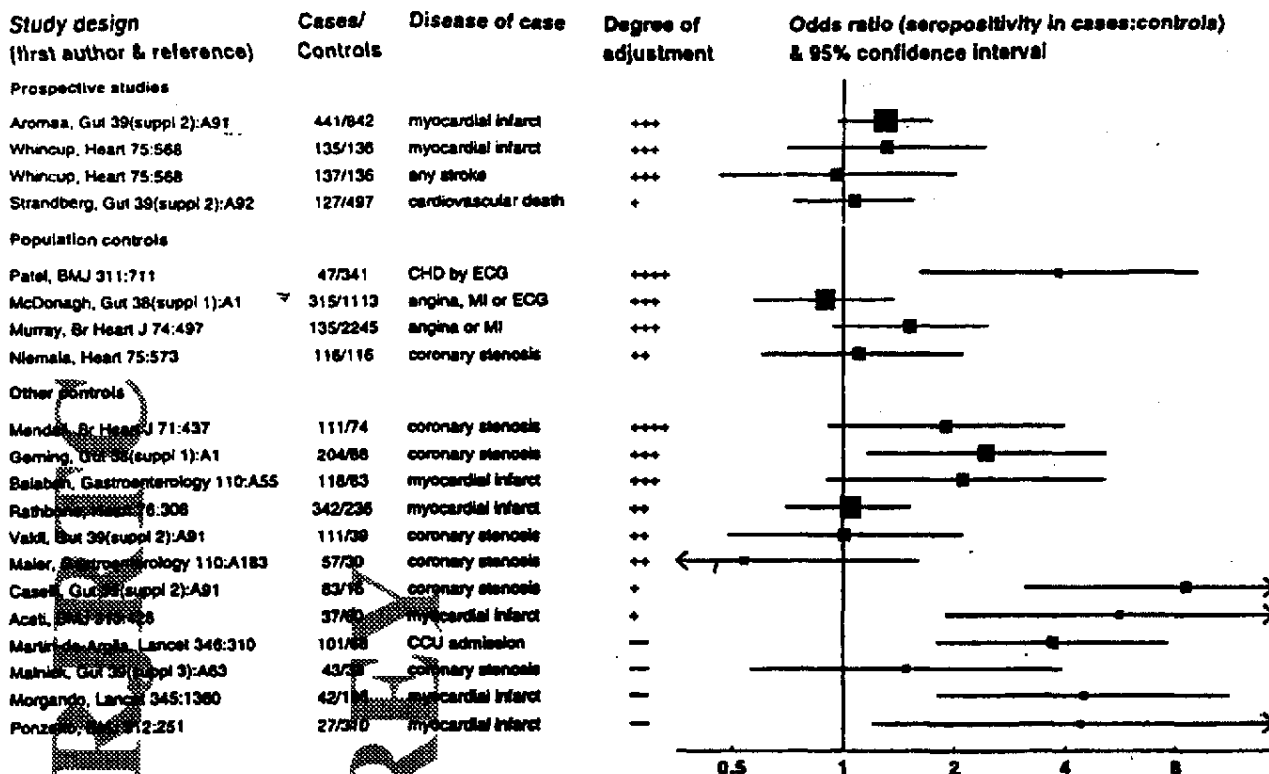


Figure 2: Odds ratios in epidemiological studies of *H. pylori* seropositivity and vascular disease

ECG=Minnesota criteria for CHD; angina=Rose angina questionnaire criteria; coronary stenosis=>50% stenosis of at least one artery; CCU=coronary care unit; MI=myocardial infarct.

the presence of *H. pylori*, *C. pneumoniae* or CMV and CHD were sought by Medline searches, scanning of relevant reference lists, hand-searching of cardiology, gastroenterology, and other relevant journals, and discussions with various investigators. Combinations of key words were used in the computer searches, including: *Helicobacter pylori*, *Campylobacter pylori*, *Chlamydia pneumoniae*, cytomegalovirus, CMV, coronary heart disease, myocardial infarction, and atherosclerosis. For all such seroepidemiological studies the odds ratio and 95% CI could be obtained from the report or the necessary information was obtained from the investigator. The following information was abstracted for these studies: the choice of controls (prospective studies with internal controls; population controls; other controls); degree of adjustment for confounders (in figures: ++=age and sex only; +++=these and some vascular risk factors; ++++=these and markers of adult socioeconomic status; ++++=these and markers of childhood socioeconomic status); and sample size. In figures 2-4 black squares indicate the odds ratio, with the square size proportional to the number

of cases, and horizontal lines represent 95% CI. Calculation of summary estimates by formal meta-analysis was not considered appropriate because of the differences in study design and degree of adjustment for confounders. (Full references for figures 2-4 are available from the authors or *The Lancet*.)

### Current evidence on *H. pylori* Epidemiological associations

Since the first report in 1994, at least 20 epidemiological studies of about 2600 cases in total have reported on the association of *H. pylori* antibody titres and either CHD (19 studies) or stroke (figure 2). The chief difficulty in trying to find out whether a causal association exists is that certain potential confounding factors, of which low socioeconomic status is a general indicator, seem to be strongly associated both with *H. pylori* infection and with CHD (table).

	<i>Helicobacter pylori</i>	<i>Chlamydia pneumoniae</i>	Cytomegalovirus
Year identified	1983	1986	1956
Type of organism	Gram-negative spiral bacterium	Gram-negative intracellular bacterium	Herpesvirus
Likely mode of spread	Faecal-oral, oral-oral	Respiratory secretions	Faecal-oral, oral-oral, parenteral
Main site of persistence	Gastric mucus layer	Alveolar macrophage	T-lymphocyte
Natural history	Persistent infection, usually from childhood	Moderately persistent; reinfections common	Persistent latent state; occasional reactivation
Antibody persistence	Persist until old age	Fluctuate with reinfection	Fluctuate with reactivation
Seroprevalence at age 50 (UK)	~40%	~50%	~50%
Correlates	Age (cohort effect); low SES	Age; periodic epidemics; Smoking; low SES	Age; low SES; immunosuppression
Associated diseases	Chronic gastritis; peptic ulcer disease; certain gastric cancers; Iron-uric dyspepsia	Pneumonia; pharyngitis; sinusitis; bronchitis; Tachycardia	Protein manifestations (eg. in adults: mononucleosis or pneumonitis)
Drug treatment	Two antibiotics (eg. amoxicillin and clarithromycin) plus proton-pump inhibitor (eg. omeprazole) for 7 days	Macrolide antibiotic (eg. clarithromycin) for 7-14 days effective in pneumonia	Ganciclovir (not curative; controls reactivation)
Vaccine	Preventive and therapeutic vaccines in early clinical trials	None yet available	Preventive vaccine of limited efficacy

SES=socioeconomic status.

References for this table are available on request from the authors or *The Lancet*.

Characteristics of three chronic infections possibly associated with vascular disease

Failure to make appropriate adjustment for potential confounders—either because they were not recorded or because they were not measured accurately (eg, long-past exposures that are related to childhood socioeconomic status<sup>19</sup>)—could lead to spurious associations of infection with CHD, or to inflated estimates of the strength of any real associations (even in studies that made adjustments for several markers of socioeconomic status). Moreover, as figure 2 shows, the 95% CI in the studies reported so far involve more than two-fold uncertainty owing to the small numbers of cases; none of the studies with more than 100 cases and 100 controls found significant associations of *H pylori* seropositivity with CHD.

Most of the studies in which controls were recruited opportunistically ('other controls' in figure 2: eg, hospital inpatients without heart disease) reported strong associations, but there was little adjustment for possible confounders in many of these studies. Studies that tried to reduce the effects of selection biases by adjusting for potential confounders and by sampling controls from approximately the same population as their cases ('population controls' in figure 2) tended to report weaker associations. Nested case-control comparisons within large prospective studies might be especially informative, since they both reduce selection biases and assess infection before the onset of clinical disease. But, although the findings in the prospective studies in figure 2 were compatible with moderate-sized effects (eg, odds ratios of about 1.5), the sample sizes were not large enough to assess such effects reliably.

Not included in figure 2 is an indirect study of *H pylori* infection in which CHD mortality in a cohort of middle-aged patients receiving antacid treatment (most of whom had peptic ulceration and would be likely to have *H pylori* infection) was found to be equal to that expected in the age-matched and sex-matched general population (in which the prevalence of *H pylori* would be about 50%).<sup>20</sup> That study did not, however, measure *H pylori* antibodies, or any potential confounders apart from age and sex. Hence, none of these studies, either separately or together, provides convincing epidemiological evidence for, or against, a causal association.

#### Pathological evidence

A few small studies reported that individuals seropositive for *H pylori* had high plasma concentrations or counts of some markers of inflammation (including fibrinogen, C-reactive protein, and leucocytes<sup>21</sup>) that may themselves be associated with increased risks of vascular disease. But, at least for fibrinogen, larger studies failed to confirm these associations with *H pylori* infection,<sup>22</sup> and, apart from weak correlations with triglycerides<sup>23</sup> and, inversely, with high-density-lipoprotein (HDL) cholesterol,<sup>24</sup> no associations have been found between *H pylori* and other vascular risk factors.

Xu and Wick<sup>25</sup> have suggested that autoimmune reactions against endogenous heat-shock protein 60 (hsp60), an endothelial antigen, could trigger atherogenesis. *H pylori* contains hsp60-like subunits, and the possibility of an association between *H pylori* infection and an immune response to hsp60<sup>26</sup> is now being investigated. There is also at least one report of

*H pylori* bacteraemia,<sup>27</sup> although any *H pylori* that penetrate beyond the gastric mucosa are likely to be killed rapidly.<sup>28</sup> Studies are now in progress to find out whether *H pylori* can be found in the walls of atheromatous arteries. But, in the only study so far published, *H pylori* DNA was not detected in any of the atherosclerotic plaques of 50 patients with abdominal aortic aneurysms.<sup>29</sup>

#### Current evidence on *C pneumoniae*

##### Epidemiological associations

Most of the 18 published epidemiological studies of *C pneumoniae* antibodies and CHD (or, in two cases, cerebrovascular disease) found at least two-fold or larger odds ratios (figure 3), and some reported increasing odds ratios with increasing antibody titres. The studies were done in different populations, used different criteria for cases, adjusted for potential confounders to differing degrees, and were, therefore, prone to different biases. The general consistency of their findings in a total of 2700 cases supports the existence of some real association between *C pneumoniae* and CHD. Residual confounding may, however, still be an explanation for at least part of the reported association, since risk factors for *C pneumoniae* infection are incompletely understood and several studies lacked adjustments for potentially important confounders, such as smoking. So far, prospective studies, which should be less liable to selection biases, have been small (figure 3).

Most of these seroepidemiological studies detected *C pneumoniae* antibodies by microimmunofluorescence, which has to be interpreted by expert microscopists and may even then have poor reproducibility.<sup>30</sup> Random measurement errors may therefore be substantial, and, owing to regression dilution,<sup>31</sup> would tend to weaken any real association. Systematic measurement errors could, by contrast, produce biases that either weaken or exaggerate the strength of any association, and only four reports indicated that disease status was concealed from microscopists. Moreover, studies that used chlamydial immune complexes or chlamydial lipopolysaccharide for detection of *C pneumoniae* infection could produce spurious associations with CHD due to cross-reactions with some antigen, such as cardiolipin, that is associated with CHD.

A further difficulty is that several of the epidemiological studies seemed to use various combinations of antibody fractions or various cut-off titres to define *C pneumoniae* seropositivity that were not chosen until an exploration of the data had shown which seemed to be most strongly related to disease. Indeed, some groups of investigators used different definitions of seropositivity in different studies (figure 3). Such post-hoc analyses could produce misleadingly strong associations, and apparently positive results from them might then have been especially likely to be published. Extreme findings in selected subgroups (such as diabetic patients, smokers, or individuals resident in certain regions) may likewise be statistically biased, especially since most subgroup analyses were based on sparse data.

##### Pathological evidence

A few small studies reported that individuals seropositive for *C pneumoniae* had high plasma concentrations of fibrinogen<sup>32</sup> or C-reactive protein,<sup>33</sup> but associations were

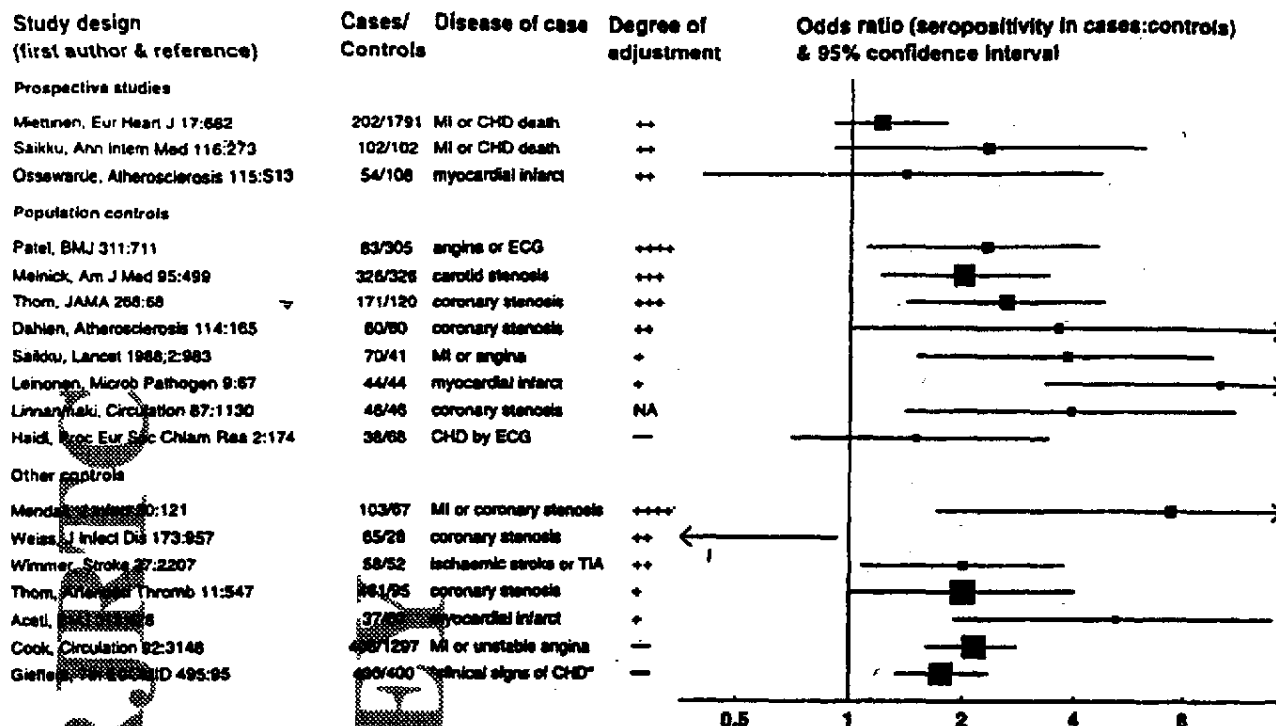


Figure 3: Odds ratios in epidemiological studies of *C. pneumoniae* seropositivity and vascular disease

Carotid stenosis—narrowing detected by duplex ultrasound imaging of artery; NA=no adjustments made although measurements were made for confounders; TIA=transient ischaemic attack. Other abbreviations and definitions as in figure 2.

not found with other vascular risk factors (such as blood cholesterol). As with *H. pylori*, *C. pneumoniae* contains hsp60-like subunits, which may indirectly trigger atherogenesis via an autoimmune reaction.<sup>4</sup> Larger studies are currently in progress to find out whether *C. pneumoniae* infection really is associated with these or other potential risk factors.

In-vitro studies show that *C. pneumoniae* is able to infect and reproduce in human smooth-muscle cells, coronary artery endothelial cells, and macrophages.<sup>5</sup> In transgenic mice, respiratory *C. pneumoniae* inoculation can induce vascular infection, with dissemination via infected macrophages.<sup>6</sup> In 18 published studies of *C. pneumoniae* in human pathology samples, evidence of presence in arterial tissue was defined as presence of chlamydial DNA, antigens, or elementary bodies.<sup>7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup> Overall, local infection was judged to be present in 52% (257 of 495) of atheromatous lesions but in only 5% (six of 118) of control samples of arterial tissue, yielding a weighted odds ratio of about 10 (95% CI 5-22). (None of these markers of local infection necessarily indicates the presence of viable bacteria, but *C. pneumoniae* has been cultured from the coronary atheromatous lesions of a patient undergoing heart transplantation.<sup>79</sup>) Owing to the difficulty of finding arterial samples completely free of atherosclerosis in older individuals, few of these studies<sup>7</sup> sampled tissue from age-matched and sex-matched controls. Nevertheless, it seems unlikely that sampling biases can entirely account for this extreme difference between case and control tissue.

Even the existence of a real association would not of itself distinguish between local *C. pneumoniae* infection predisposing to atheroma, and the reverse sequence. The detection of *C. pneumoniae* DNA in other non-respiratory sites<sup>7</sup> (such as stenosed aortic valves, hepatic vessels, spleen, and skin granulomata) has led to

suggestions that the organism may be merely an "innocent bystander" in inflamed tissue. Conversely, *C. pneumoniae* in coronary arteries might promote local injury and elicit an autoimmune inflammatory response.<sup>4,20</sup> Hence, the hypothesis that *C. pneumoniae* may be causative of arterial disease remains plausible but unproven.

### Current evidence on cytomegalovirus and other herpesviruses

#### Epidemiological associations

Two-fold or larger odds ratios have been reported in several epidemiological studies of CMV antibodies and cardiovascular disease (figure 4). Some of these reports described increasing odds ratios with increasing antibody titres or with the severity of the atherosclerosis, which strengthen the plausibility of the associations. However, these studies of CMV, even more than those of *H. pylori* or *C. pneumoniae*, were characterised by small sample sizes, incomplete adjustments for known confounders, and exploratory statistical analyses. Furthermore, few were of classic CHD: more than 1200 of the 1600 cases in these studies were defined on the basis of coronary restenosis after atherectomy, or the development of lesions in transplanted hearts or in arteries outside the coronary circulation (figure 4). So, even if CMV does cause such lesions, the infection may not be relevant to native coronary-artery atherosclerosis.

Although herpesviruses other than CMV might be associated with human atherosclerosis,<sup>8</sup> the presence of antibodies to herpes simplex virus types 1 and 2 has not generally been associated with cardiovascular disease in epidemiological studies.<sup>8</sup> Moderate-sized effects may, however, have been missed in populations with very high (eg, 90%) rates of seropositivity to herpes simplex

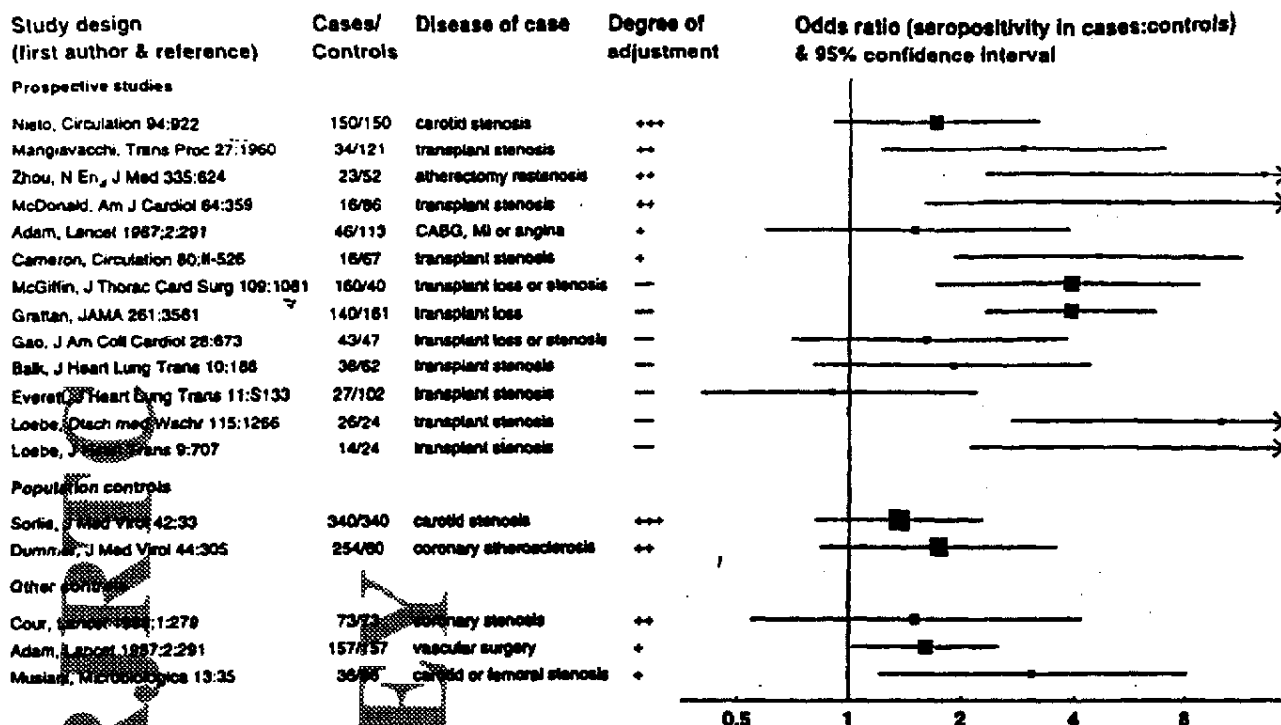


Figure 4: Odds ratios in epidemiological studies of CMV seropositivity and vascular disease

Angina=positive ECG exercise test; coronary stenosis>=50% stenosis of at least one artery, including after atherectomy or heart transplantation; CABG=coronary-artery bypass graft; atherectomy=confirmed by histology; transplant loss=patient's death or heart retransplantation; vascular surgery=CABG, carotid endarterectomy, femoral, iliac, or abdominal aortic surgery. Other abbreviations and definitions as in figures 2 and 3.

Virus" in studies that used unreliable proxies of infection (eg, a history of cold sores<sup>21</sup>).

#### Pathological evidence

Little evidence has been reported on CMV titres and classic vascular risk factors or plasma markers of inflammation, although some herpesviruses can alter cholesterol metabolism in smooth-muscle cells, activate various cytokine factors, and elicit the expression of cytokines, chemokines, and cellular adhesion molecules from the vascular wall.<sup>1,2</sup> In the 16 published studies of CMV pathology samples there were only small differences in the proportion of atheromatous and non-atheromatous blood vessels positive for CMV (47% [283 of 606] vs 39% [154 of 398]), with a weighted odds ratio of about 1.4 (95% CI 1.0-1.9).<sup>28,31-37</sup> But, even if CMV infection initiated the process of plaque formation, the infectious agent might not remain detectable. For example, in a chicken model, viral antigen could be found in smooth-muscle cells in early arterial lesions but only at the periphery of plaques in advanced lesions.<sup>38</sup> Moreover, even if low-grade infection does persist, it may not be detected unless a sensitive test is used, such as one based on the polymerase chain reaction (PCR). For example, in one study of 70 arterial samples, CMV genome was detectable in 70% by PCR but in only 20% by dot-blot hybridisation.<sup>39</sup> Overall, in the pathology studies that used PCR, CMV was detected in 57% (228 of 399) of atheromatous vessels compared with 36% (113 of 311) of control samples, yielding a weighted odds ratio of about 2.5 (95% CI 1.6-3.8). Although this odds ratio is conventionally significant, it is not very high and the 95% CI is wide, so it does not provide convincing evidence as to the relevance of CMV to atherosclerosis.

Some features of atherosclerosis resemble benign neoplasia,<sup>40</sup> and herpesviruses can help induce genomic transformation.<sup>41</sup> CMV has been studied in relation to p53,<sup>42</sup> a protein that is indirectly involved in DNA repair; inactivation or loss of p53 is commonly one of the early stages in the production of a human cancer cell. One of the major proteins produced by CMV binds to, and inactivates, p53.<sup>43</sup> In patients who have just undergone coronary angioplasty, infection of smooth-muscle cells by CMV that inactivates p53 is associated with cellular proliferation that can lead to coronary restenosis.<sup>44</sup> This finding raises the possibility that a similar mechanism might underlie primary atherogenesis. The possible relevance of CMV to arterial lesions is also supported by findings that neointimal proliferation in CMV-infected rats is increased after vascular injury,<sup>45</sup> but not by a report that no CMV mRNA was found in atherectomy samples from 40 patients.<sup>46</sup>

#### Future studies

##### Observational studies

Epidemiological studies of infections and CHD are needed. These studies should be large enough for moderate-sized effects to be assessed or refuted reliably, and involve repeated antibody measurements in at least a subsample to allow correction for regression dilution.<sup>47</sup> In such studies, the effects of residual confounders need to be kept to a minimum, for example by investigation of socially homogeneous populations (such as doctors) or age-matched and sex-matched sibling-pairs (one with and one without CHD). Sibling-pair studies would, however, need to be especially large, since many of the pairs would probably share the same infection status.<sup>48</sup> If such studies measured antibodies to several agents (including some not thought to be related to CHD) in

the same individuals, and much stronger associations were found with certain infections (for example, cytotoxin-positive strains of *H pylori*) than with others, bias could less plausibly explain the findings. Studies in young adults might be especially informative, since the associations of vascular risk factors with CHD tend to be stronger in younger than in older individuals.

Further seroepidemiological studies could also help to investigate possible causative mechanisms by comparison of plasma concentrations of inflammatory markers and other possible vascular risk factors in individuals seropositive and seronegative for particular microorganisms (as well as before and after anti-infective treatment), and by correlation of antibody titres with evidence of infection in the arterial walls of the same individuals (especially since a few studies have suggested that *C pneumoniae* titres are not positively associated with the presence of chlamydia in atherosclerosis). Pathology-based studies that compare the frequency of infections in arterial lesions of varying macroscopic or histological grades might help clarify the sequence of *C pneumoniae* infection and atherosclerosis, and assess the role of CMV at various stages of atherogenesis.

#### Intervention studies

The relevance of infections to CHD may well need to be studied not only by observational studies but also by small-scale randomised trials of the effects of antibacterial and antiviral treatments on possible mediators of disease (eg, inflammatory markers) and by large-scale randomised trials of CHD prevention. But, even if some chronic infections are causally linked with CHD, the effects of these infections on CHD risk might not be rapidly and fully reversible. Hence, trials of interventions against infections might need to randomise large numbers of individuals and to observe them for some years to assess reliably the moderate effects on CHD that are plausible. Given the tentative nature of the current evidence for associations of infections with CHD, the most appropriate research strategy might be to factor such assessments into existing trials of unrelated interventions among people at high risk of CHD with long-term follow-up, and to test interventions that might be effective against more than one infection (eg, regimens including clarithromycin may eliminate not just *H pylori* but also *C pneumoniae*). If such trials randomised individuals irrespective of antibody status, with baseline blood samples stored for future testing either for all patients or for a retrospective case-control subset, any improved assay methods available only at the end of the trial (including, for example, novel techniques to identify different bacteria or bacterial subtypes) could then be used.

#### Conclusion

The available evidence about chronic infections and CHD is still sparse and its interpretation is limited by potential biases. For *H pylori*, residual confounding by causal risk factors may account entirely for the rather weak epidemiological associations that have been reported. For *C pneumoniae*, the evidence of association is stronger, but the temporal sequence of infection and CHD is uncertain. For CMV, only a limited number of patients with classic atherosclerotic CHD have been

studied. Some of these uncertainties may be resolved by better and larger seroepidemiological or pathology-based studies, but randomised intervention studies may eventually be needed.

We thank Colin Baigent, Valerie Beral, Robert Clarke, Richard Doll, Ken Fleming, Anthony McMichael, John Muir, Andrew Neil, David Strachan, Michael Ward, and Martin Vessey for helpful comments; Paul Appleby for plotting the figures; and Carsten Flohr for translating German publications.

JD was supported by a Rhodes Scholarship and a Balliol College Senior Scholarship, and RC holds a British Heart Foundation professorship.

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## COMMENTARY

## Can we treat coronary artery disease with antibiotics?

See pages 404 and 432

Atherosclerotic vascular disease and its manifestations remain the scourge of the modern world. Conventional risk factors, such as smoking, diabetes, hypertension, lipids, and lifestyle, do not fully explain the diversity of this disease and why interventions have not reduced its incidence as much as epidemiologists have predicted. One should therefore think laterally.

In the pathogenesis of thrombosis, Virchow's triad is satisfied by three broadly independent factors—slowing of blood flow (viscosity), changes in blood constituents (abnormal clotting factors and platelet activation, leading to a hypercoagulable state), and changes in the vessel wall (endothelial damage or dysfunction). Thrombogenesis is intimately related to atherogenesis, and the abnormalities described above have been examined by many workers to explain how risk factors lead to atherosclerosis. For example, smoking contributes to endothelial damage, hypercoagulability, and platelet activation.

Chronic infections can increase hypercoagulability, by inducing hyperfibrinogenemia (and therefore also hyperviscosity), and if particular infections also cause endothelial damage or dysfunction, the key components leading to atherogenesis are present.<sup>1,2</sup> Chronic infections and atherosclerosis also have uncanny similarities to a chronic inflammatory process, with activation of macrophages and increased cytokine production.<sup>1,2</sup>

*Chlamydia pneumoniae* is an intracellular organism that has been shown in case-controlled studies to be associated with coronary artery disease, atherosclerotic carotid disease, and stroke.<sup>3,4</sup> But whether *C. pneumoniae* is an innocent bystander or whether it is a vicious assassin, causing endothelial damage, hypercoagulability, and macrophage activation, remains uncertain. For example, macrophages may ingest *C. pneumoniae* particles in the lung or elsewhere before migrating to atheromatous lesions, in which case it is a bystander. By contrast, *C. pneumoniae* infection may actively induce immune activation, cytokine release, endothelial damage, and thrombogenesis, actively leading to atherogenesis.<sup>5</sup>

In this issue of *The Lancet*, the Roxis study group report the effects of giving roxithromycin, an antichlamydial macrolide with supposed antiinflammatory properties, to patients with unstable angina or non-Q-wave myocardial infarction. The composite triple endpoint (death, acute myocardial infarction, and recurrent angina) was reduced in the treatment group (1% vs 9% in the placebo group,  $p=0.018$ ). However, this study does not examine response to antibiotics according to whether patients were seropositive to *C. pneumoniae* (only 47% of patients in the treated and 49% in the placebo group were seropositive),

nor does it explore the changes in markers of inflammation, thrombogenesis, or endothelial dysfunction. In a similar study but one targeting treatment at seropositive patients rather than using the blanket approach adopted in Roxis, Gupta et al<sup>6</sup> found that raised antibody titres to *C. pneumoniae* were predictive of cardiovascular events (odds ratio 4.2, 95% CI 1.2 to 15.5,  $p=0.03$ ), and that lowering of the risk of these events by azithromycin was accompanied by a decrease in antibody titres. Gupta et al<sup>6</sup> have also reported preliminary findings that azithromycin therapy reduced monocyte activation, but not procoagulant markers, at 6 months.

Is eradication of chlamydia likely to be a means of secondary prevention of coronary artery disease? Although the findings are encouraging, they come from small pilot studies. Large randomised, double-blind, placebo-controlled studies are needed, to establish the precise value of antibiotic eradication therapy, at least in patients seropositive for infection. And perhaps it was not eradication of the organism but other properties of the antibiotics used in the two trials, such as broad actions against other infectious organisms, and antiinflammatory, antioxidant, or antithrombotic effects (all of which may or may not be fully characterised) that were responsible for the positive effects.

Many other issues need to be explored. One is the relation between *C. pneumoniae* infection and different ethnic groups because there is some evidence of different rates of infection among whites, blacks, and Indo-Asians.<sup>7</sup> Another is whether acute or chronic infections initiate thrombogenesis and atherogenesis. We also need more data on women, especially since the study by Gupta et al<sup>6</sup> was conducted wholly among men and the Roxis study was done predominantly (>70%) in men. The review by John Danesh and colleagues in this issue of *The Lancet* explores some of the evidence for the associations between chronic infections and coronary heart disease and justifiably concludes that much of the evidence still remains sparse and open to many potential biases. The possibility of more than one organism—for example, *C. pneumoniae* and *Helicobacter pylori*—being guilty in a synergistic manner also cannot be excluded. Further study of the mechanisms by which suspect organisms result in abnormal thrombogenesis and atherogenesis, the (beneficial) influence of antibiotic therapy, and the effects of ethnicity or gender, are therefore needed.

Evidence for the value of antibiotic intervention in chronic disease is already available for *H. pylori* eradication therapy in preventing peptic ulcer disease, at least in patients with evidence of such infection. If specific anti-

chlamydial eradication therapy is confirmed as being able to reduce cardiovascular events, the day may come when a post-myocardial infarction patient with *C. pneumoniae* infection would be on a regimen of aspirin, beta-blocker, angiotensin-converting-enzyme inhibitor, statin, antioxidants, and antibiotic. Efforts to help such patients comply with treatment may then well be needed.

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## Reversibility of rise in Russian mortality rates

See page 353

Striking changes in mortality rates have been observed in Russia recently. Between 1984 and 1987 life expectancy at birth increased from 61.7 to 64.9 years in males and from 73.0 to 74.3 years in females. In 1987-94 life expectancy declined sharply by 7.3 years for males and 3.3 years for females. In today's *Lancet* D A Leon and colleagues argue that these large changes in life expectancy cannot be due to artefacts in the mortality data because age-specific mortality rates for neoplasms remained unchanged during this period.

Information on mortality rates in Europe has been collected for a collaborative project to describe spatial variations, by age and sex, in all-cause and selected cause-specific mortality rates across Europe, taking into

Age-standardised all cause\* mortality in males; 1990-91



Rates classified by percentiles, which are population weighted. The groups are below 10th percentile, 10th to <25th, 25th to <40th, 40th to <60th, 60th to <75th, above 75th. \*ICD 001-0999

consideration the subnational patterns and their continuity across country borders. Mortality data were collected for the years 1980-81 and 1990-91.

There were wide variations in all-cause mortality rates in 1990-91, with a distinct east-west pattern of high mortality in central and eastern Europe and low mortality rates in western Europe. The largest differences in mortality rates were among men, with the all-cause mortality rates being almost twice as high in eastern as in western Europe. Similar but less pronounced differences were observed among women.

Analyses of changes in age-standardised all-cause mortality rates show that in western European countries all-cause mortality rates declined between 1980-81 and 1990-91. In central European countries (eg, Poland, Hungary, Czech Republic) relatively small changes were observed during this period. However, since 1987 all-cause mortality rates rose considerably in Russia. If regional mortality data had been available for 1994, the picture would have been even more striking than that shown in the figure, which represents mortality data collected in 1990-91.

Leon and colleagues report that mortality rates rose most among those aged 20-69. The changes were strongest for alcohol-related diseases. In 1987 accidental poisoning by alcohol accounted for over 80% of deaths among men aged under 45. The consumption of pure alcohol per head in Russia in 1993 was 14.5 L of pure alcohol per year, or 40 g of pure alcohol per day. With such a high level of consumption, the population burden of alcohol-related diseases and death due to accidents and violence, strokes, arrhythmias, and cardiomyopathies is bound to be high.

A survey carried out in 1992 and 1993 showed that 82% of the men consumed alcoholic drinks, the average intake of pure alcohol among the alcohol consumers was about 60 g/day. This is equivalent to about 420 kcal/day. If average energy intake for men aged 20-69 is about 2500 kcal/day, 17% of energy would come from alcohol. Together with a high intake of saturated fat and a low intake of antioxidants, due to a low intake of vegetables and fruits, the diet would be unbalanced and atherogenic. Such a diet, together with a high prevalence of smoking and drinking, can account for the high mortality rates due to cardiovascular disease in central and eastern European countries such as Hungary and Russia.

Changes in environmental determinants of diseases will rapidly lead to changes in mortality rates, as was shown by the effects of the then USSR's President Gorbachev's anti-alcohol campaign in 1985. Also, changes in dietary and smoking habits between 1972 and 1992 in Finland led to a 50% reduction in age-standardised deaths from coronary heart disease. These findings show that the appalling life expectancies in Russia of 57.6 years for men and 71.0 years for women can soon be improved by measures such as preventing alcohol abuse, discouraging smoking, and encouraging a healthy diet. To make any impact, these measures should be included immediately in the socio-economic reform now taking place in Russia.

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The inherent virtues of managed care have manifested themselves in many salutary improvements to the system that might otherwise never have been made. These include attempts to eliminate waste and redundancy, a greater focus on health promotion and disease prevention, more attention to the management of chronic diseases, a focus on the accountability of physicians and health plans and on the quality of care, lower hospitalization rates without an obvious decline in the quality of care, heavy investment in patient-information systems, and — at least for the present — control of employers' health care costs.

The perverse effects of managed care are many and have been detailed elsewhere. In fact, managed care has dealt rather ineffectively with its shortcomings, generating a backlash that has resulted in anti-managed-care legislation. State and federal laws specifying lengths of stay for deliveries and mastectomies, limiting emergency care, and making gag rules illegal are but a few examples. Yet, regulation of managed care and the market in medicine has lagged. As compared with hospitals, which are governed by gargantuan regulatory structures, the multiplayer managed-care behemoths are virtually unregulated. This leaves the amoral and impersonal mechanisms of the market to determine how care is delivered.

Because of the rapid rate of change, the extent of change, and the strong market forces driving change, predictions of the future seem less certain than they used to. But I think managed care is likely to have a stronger presence in the future than Ginzberg and Ostrow predict. To survive, however, managed-care plans will have to show that they have become better business: that they care about more than profits, that they do not skimp on care, that they support their fair share of teaching, research, and the care of the poor, that they no longer muzzle physicians, and that they offer something special (including control of costs) by managing care.

I believe that the homogenized one-model-fits-all, gatekeeper-controlled approach to health care is a failed experiment and that in the long run care that is tailored to the needs of the individual will win out. This will mean assigning the most appropriate personnel to provide the care needed by individual patients. For some patients, that will be a primary care physician alone; for others, only a specialist; for some, it might be a nurse practitioner, together with a primary care physician and a specialist; and for those with complex illnesses, it might be a care manager, coordinating the care given by several specialists and a generalist. No matter who provides the care, however, it will never be complete unless those responsible for it seek a far deeper understanding of the patient's social, economic, and ecological contexts than we do now. Becoming more aware of the psychological and personal barriers to effective care is an essential part of this kind of care.

In a talk at the 1994 Institute of Medicine meeting, a colleague of mine who was asked to speculate about how medical care would be organized five years hence summed up the status of predictions: he said he wasn't even sure what the system would be like when he got back to his office that afternoon.<sup>10</sup> The lesson is that all predictions (including mine) should be taken with a grain of salt.

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## INFLAMMATION, ATHEROSCLEROSIS, AND ISCHEMIC EVENTS — EXPLORING THE HIDDEN SIDE OF THE MOON

CARDIAC and cerebral ischemic events develop unpredictably in patients with widely varying degrees of atherosclerotic disease. Thus, a major area of research is the study of the stimuli that provoke ischemic events. The weak relation between ischemic events and flow-limiting stenoses in the coronary and carotid arteries leaves room for innovative research.<sup>1</sup> However, it is easier to study the details of accepted paradigms than it is to develop new hypotheses, just as it was easier to map the visible face of the moon than it was to explore its hidden side.

The study by Ridker et al. in this issue of the *Journal*<sup>2</sup> provides convincing evidence that among normal men, base-line serum levels of C-reactive protein are predictive of future myocardial infarction and ischemic stroke but not of venous thrombosis. The risk increased with rising levels of C-reactive protein, even when the values were within the normal range. The increased risk was independent of lipid-related and non-lipid-related cardiovascular risk factors and was reduced by treatment with aspirin in direct proportion to the base-line C-reactive protein value.

This observation, made in men with favorable

coronary-risk-factor profiles, expands on the results of previous reports showing the long-term prognostic value of C-reactive protein levels in people with multiple risk factors<sup>3</sup> and in patients with chronic angina.<sup>4</sup> The long-term prognostic value of C-reactive protein levels, even when they are within the normal range, and the short-term prognostic value of elevated C-reactive protein levels during hospitalization in patients with unstable angina<sup>5</sup> may open new avenues for research on the stimuli leading to irreversible ischemic events.

Elevated serum levels of C-reactive protein are nonspecific but sensitive markers of the acute-phase response to infectious agents, immunologic stimuli, and tissue damage. The long-term prognostic value of C-reactive protein levels<sup>2</sup> may be related to chronic infection of the vessels with organisms such as cytomegalovirus, chlamydia, and helicobacter, but it seems unlikely because the risk association was found for values obtained in 90 percent of normal people and was sustained over several years. In our own studies, my colleagues and I found no evidence of replicating cytomegalovirus in endarterectomy specimens from unstable coronary plaques,<sup>6</sup> but we have found an abnormal immunologic response in patients with unstable angina and elevated C-reactive protein levels<sup>7</sup> that was consistent with previous reports of leukocyte activation in unstable angina.

The elevated levels of C-reactive protein in patients with unstable angina and those on admission in patients with myocardial infarction preceded by unstable angina<sup>8</sup> were not related to myocardial necrosis, because patients with elevated levels of troponin-T were excluded<sup>5</sup> and because elevated levels of C-reactive protein may persist for three months after the resolution of symptoms in nearly 50 percent of cases.<sup>8</sup>

The prognostic value of a marker such as C-reactive protein is likely to become apparent only when the levels of other determinants of risk are low. The levels of traditional coronary risk factors were low in the Physicians' Health Study,<sup>9</sup> and patients with severe persistent unstable angina who were studied by Luzzo et al.<sup>5</sup> had good left ventricular function and were less than 70 years old — characteristics that are associated with a favorable outcome. It is possible that C-reactive protein levels may have less prognostic value in patients with a large number of risk factors.

The observation that most infarct-related arteries have no flow-limiting stenoses is driving the search for inflammatory mechanisms of acute myocardial ischemia.<sup>9</sup> Metalloproteinases released by inflammatory cells can lead to fissuring of coronary atherosclerotic plaques, although in one study no fissuring was found in 40 percent of the inflamed plaques beneath infarct-related thrombi.<sup>10</sup> Conversely, coronary-plaque fissuring occurs in 10 to 25 percent

of noncardiac deaths.<sup>1</sup> Finally, inflammatory-cell infiltrates are commonly found in chronic atherosclerosis, and evidence of immunologic activation in plaques can be found in both acute<sup>10</sup> and chronic ischemic syndromes.<sup>11</sup> Common findings cannot, by themselves, explain the occasional occurrence of ischemic events.<sup>1</sup>

Myocardial infarction and ischemic stroke are the end result of sudden, persistent interruption of regional blood flow from any cause, such as thrombosis, spasm, small-vessel constriction, or a combination of all three. In turn, there may be multiple causes of thrombosis, spasm, and small-vessel constriction.<sup>1</sup> Inflammation is only one of the components that may favor the development of acute ischemic events. C-reactive protein levels are normal in 40 percent of patients with unstable angina and in patients with myocardial infarction not preceded by unstable angina. Conversely, in other vascular disorders C-reactive protein levels may remain elevated for years in patients who never have a myocardial infarction or stroke.<sup>12</sup> The progressive reduction of the risk of myocardial infarction in patients with high C-reactive protein levels who are treated with aspirin may suggest a beneficial antiinflammatory effect of the drug that becomes detectable in low-risk patients. This possibility deserves appropriate attention.

The intriguing findings of Ridker et al.<sup>2</sup> suggest that the time has come to reexamine the pathogenetic components of myocardial infarction and ischemic stroke in the hope of identifying the patients who would benefit most from particular therapies. At present, all patients with unstable angina are treated with the latest antithrombotic drugs, all patients with acute myocardial infarction are treated with ever more efficacious thrombolytic agents, and all patients with hypercholesterolemia are treated with cholesterol-lowering drugs. Just as people with very low C-reactive protein levels may not benefit from prophylactic aspirin, patients with coronary disease who are in the top third of cholesterol levels but in the lowest third of C-reactive protein and fibrinogen levels may not benefit from cholesterol reduction, since such patients have been reported to have no ischemic events over a two-year follow-up.<sup>4</sup> Ischemic heart disease is appearing to be an ever more complex syndrome, like anemia. Patients with severe anemia, whatever the cause, benefit from blood transfusions, but indiscriminate treatment of anemic patients with iron is clearly poor medical practice. The search for the multiple pathogenetic components of acute ischemia is a major challenge. Different pathogenetic mechanisms are likely to require different therapeutic approaches.

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## ADJUVANT THERAPY FOR RECTAL CANCER — A GOOD FIRST STEP

THE usual initial treatment for patients who present with clinically resectable rectal cancer is surgery. Adjuvant therapy for this disease has improved considerably in the past decade, and most clinical trials now focus on postoperative combination therapy. The two components of this therapy are pelvic irradiation and chemotherapy based on fluorouracil. Radiation therapy decreases the incidence of local (pelvic) recurrences; chemotherapy enhances the effects of radiation and improves survival by decreasing the risk of distant metastasis.

The publication of two randomized trials in which significant improvement in local control and survival was found with postoperative combination therapy<sup>1,2</sup> prompted a National Cancer Institute Consensus Conference in 1990 to recommend that standard postoperative adjuvant treatment for patients with tumors extending into the perirectal fat (stage T3), with involvement of the mesorectal or pelvic lymph nodes (N1 through N3), or both should be six cycles of fluorouracil-based chemotherapy plus con-

current pelvic irradiation.<sup>3</sup> Since that time, trials of postoperative therapy have concentrated on identifying optimal chemotherapeutic drugs and improving methods of administration.

Postoperative combination therapy is usual for resectable rectal cancer in the United States, but it is not routine in some European countries, where chemotherapy is considered investigational and radiation therapy is delivered preoperatively in an intensive, short course. These differences have long been a source of controversy with our European colleagues.

There have been 10 modern randomized trials of preoperative radiation therapy for resectable rectal cancer.<sup>4</sup> Most used an intensive, short course of irradiation. Five reported a significant decrease in the rate of local recurrence. Some found a significant improvement in survival in subgroup analyses, but none have shown a significant advantage for the whole group of treated patients.

The final results of the Swedish Rectal Cancer Trial appear in this issue of the *Journal*.<sup>5</sup> This is one of a series of randomized trials performed by a group of respected investigators from Sweden. It is the first randomized trial of intensive, short-course preoperative radiation therapy to show a survival advantage for the total patient group, according to an intention-to-treat analysis. As compared with postoperative combination therapy, a short, intensive course of preoperative irradiation is more convenient for the patient and less expensive. Patients receive therapy in only 5 fractions (administered during one week), as opposed to 28 fractions (over six weeks), and do not need six months of chemotherapy. If the one-week course of preoperative radiation therapy significantly improves survival, why not adopt this as the standard of care?

Given that the other nine randomized trials of preoperative radiation therapy have not found a survival benefit, the Swedish data need confirmation. Moreover, even if future trials confirm the survival advantage, other issues — such as treatment end points and toxicity — need to be addressed. The primary end point of most clinical trials in patients with cancer is survival. This measure of success is important, but there are other pivotal end points in the treatment of rectal cancer, including local tumor control, preservation and function of the sphincter, and quality of life. In our quest to improve overall survival, we sometimes overlook these matters.

A major goal of preoperative radiation therapy is the preservation of the sphincter. Two trials<sup>6,7</sup> have reported preliminary results of preoperative radiation therapy in patients who were prospectively examined by a surgeon before the start of radiation therapy and were declared to need abdominoperineal resection. Neither trial used chemotherapy. After preoperative irradiation, approximately 80 percent of the patients were able to undergo sphincter-pre-